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PULMONARY SIDEROSIS

TWO CASES WITH RETICULO-ENDOTHELIAL SIDEROSIS *

MILTON G. BOHROD, M.D.

DECATUR, ILL.

Pulmonary diseases due to inhaled solid substances in fine suspension have been known for many years, although scientific studies date back only to 1867, when Zenker [1] described two cases of what he named siderosis and proposed for the entire group of dust diseases the term pneumonoconiosis. Of the types included in the latter term, only anthracosis and silicosis, the most common, have been adequately studied.[2] Siderosis, first described, is less common, and while clinical and roentgenologic studies on metal workers and iron miners abound, pathologic studies still cover only about thirty cases.

Before methods of reducing the amounts of dust in mines and factories were in common use, pulmonary disease was exceedingly common among the workers in these establishments. Hirt (quoted by Jötten and Arnoldi [2]) estimated that 53.3 per cent of metal workers had lung trouble, and that of these 28 per cent were tuberculous. Among 100 drillers in iron mines, Cronin [3] found a large proportion with symptoms related to the respiratory system, although only 30 per cent gave abnormal physical signs. Even now, in spite of the improvement in working conditions and the reduction of the amounts of dust, there are still sufficient cases to warrant intensive study of the dust hazards. In part, this is due to the imperfections or insufficient use of dust-diminishing apparatus, but another potent factor is the "latent period" in pneumonoconiosis (Watt, Irvine, Johnson and Steuart [4]), so that persons exposed years ago are only now developing dangerous symptoms.

* Submitted for publication, Feb. 14, 1930.

* From the Department of Pathology and Bacteriology, University of Illinois College of Medicine.

1. Zenker, F. A.: Ueber Staubinhalationskrankheiten der Lungen, Deutsches Arch. f. klin. Med. **2**:116, 1867.

2. For complete reviews of the literature on pneumonoconiosis see:
Jötten and Arnoldi: Gewerbestaub und Lungentuberkulose, Berlin, Julius Springer, 1927.
Ickert, F.: Staublunge und Staublungentuberkulose, Berlin, Julius Springer, 1928.

3. Cronin, A. J.: Dust Inhalation by Hematite Miners, J. Indust. Hyg. **8**:291, 1926.

4. Watt, A. H.; Irvine, M. A.; Johnson, and Steuart, W.: General Report of the Miner's Phthisis Prevention Committee, appendix no. 6, Pretoria, 1916, p. 81.

The amounts of metallic substances recoverable from the lungs of miners, metal workers and others long exposed to a dusty atmosphere are surprisingly large. Langguth [5] found 7.9 per cent of the dry weight of a siderotic lung to be iron oxide. In silicosis, the amount is much higher (over 23 per cent, according to Oehmann,[6] and from 7.4 to 39.8 per cent, according to Riddle and Rothwell [7]). But the amounts of dust to which such persons are exposed are also large. Ickert [2] estimated that a miner in Mansfield inhales from 48 to 480 Gm. of dust in the course of forty years of employment. In a hematite mine, at least 56 per cent of the dust is iron sesquioxide (Cronin [3]).

The reproduction of siderosis in animals has not met with much success; a typical siderosis has never been produced. Carleton [8] exposed guinea-pigs to far more massive doses of hematite and iron dusts than are ever encountered industrially, with no definite pathologic results. With the former dust, only a little bronchitis was noted. Iron dust in large doses caused death from a toxic influence; in smaller doses, it caused some bronchitis, but no induration. His conclusion from these experiments that these dusts do not constitute serious hazards is not warranted in view of the difficulty with which animals develop pneumonoconiosis and in view of Cronin's analysis [3] of the great incidence of symptoms and pathologic changes in workers with hematite. Other experimenters have found only slight fibrosis following long exposures of animals to dust-laden air, with a high grade proliferative reaction of endothelium and lung capillaries (see the summary of the experimental work by Jötten and Arnoldi [2]). In such experiments, the right lung has been found to contain more dust than the left, the apexes more than the bases (Ickert [2]). The reasons advanced for the failure of experimental animals to develop pneumonoconiosis have generally had to do with the difference of attitude, the erect position of man favoring the settling of dust in the lower air passages. In the light of such unsatisfactory evidence obtainable from experiments on animals, human material, clinically and at necropsy, offers a more fertile field for investigation.

While differences in the pathologic picture of pneumonoconiosis have long been recognized, and the nature of the dust concerned has been considered an important factor in determining the kind and the

5. Langguth, F.: Ueber die Siderosis Pulmonum, Deutsches Arch. f. klin. Med. **55**:255, 1895.

6. Oehmann, R. C.: Ueber die pathologische Anatomie der Silikose, Acta tuberc. Scandinav. **4**:67, 1928.

7. Riddle, A. R., and Rothwell, H. E.: Some Clinical and Pathological Observations on Silicosis in Ontario, J. Indust. Hyg. **10**:147, 1928.

8. Carleton, H. M.: The Effects Produced by the Inhalation of Hematite and Iron Dusts in Guinea Pigs, J. Hyg. **26**:227, 1927.

degree of involvement, such differences have not been studied minutely enough. This is perhaps due to the fact that the overwhelming number of cases of pneumonoconiosis have been due to silicates, and only this type has been adequately studied. A less common but no less interesting type is due to the inhalation of dusts containing iron. Zenker's report,[1] which first recognized the importance of dust diseases, was of such a case. Merkel [9] several years later reported nine such cases. But, in all, the reports on siderosis still concern only about thirty cases.

Two types of dust contain iron in considerable quantities. The first is found in iron ore mines and in factories using certain iron pigments (English red). The usual form of this iron is the oxide. The second type is found in metal grinding and polishing establishments where tiny particles of metallic iron are removed from the products manufactured and blown into the air. In these establishments, the air also contains large quantities of silicates removed from the grindstones.

Hart [10] has described two kinds of siderosis. The first, which he calls the red type of iron lung, is the result of the first type of dust. In this type, pneumonoconiotic induration predominates, and there is little tuberculosis. The other, the black type, is found in metal grinders and polishers; the indurative process is less pronounced and tuberculosis is unrestrained. In this type the mortality from tuberculosis is high.

The two cases here presented illustrate these two types of siderosis.

REPORT OF CASES

CASE 1.—*History.*—A colored man, aged 37, who worked as a metal polisher in a machine shop, entered the hospital on Sept. 11, 1928. For six or eight months he had been growing progressively weaker, so that he worked only for short periods. During this time, he had lost about 25 pounds (11.3 Kg.). He had severe cough which was productive of much sputum, but he had never expectorated blood. His appetite was poor. For three months he had been short of breath and had had fleeting pains in the chest, abdomen and flanks. He had had typhoid fever and malaria at the age of 12 and pleurisy in both sides a year before entrance. Fourteen months previously, he had had a peritonsillar abscess. He had had gonorrhea and a bubo, which had been incised, but he said that he had not had a syphilitic infection. One brother died of tuberculosis at the age of 28.

Physical Examination.—The patient showed large tonsils. Expansion of the lungs on both sides was poor. Dulness was present over both lungs, especially over the apexes. The breath sounds were increased throughout. He had anemia (hemoglobin, 55 per cent; red blood cells, 3,650,000). The Wassermann and Kahn reactions were three plus. A roentgenogram showed diffuse infiltration in both lungs with probable cavity formation. The temperature went up to about

9. Merkel, G.: Die tuberkulose Erkrankung siderotischer Lungen, Deutsches Arch. f. klin. Med. **42**:179, 1888.

10. Hart, C.: Die anatomischen Grundlagen der Disposition der Lungen zu tuberkuloser Erkrankung, Ergebn. d. allg. Path. u. path. Anat. **14**:405, 1910.

100 F. in the afternoon. The clinical diagnosis was advanced pulmonary tuberculosis, and tubercle bacilli were found in the sputum.

Course.—The patient's condition remained the same until December 23; then, in the evening, the temperature suddenly went up to 104 F. Râles were found throughout the thorax and evidence of cavitation in both upper lobes. He coughed considerably and expectorated about a cupful of sputum daily. With only occa-

Fig. 1 (case 1).—Cut surface from the right lung.

sional days of normal temperature, he grew progressively weaker, until he died on March 14, 1929.

Necropsy.—Necropsy was performed within an hour after death. The body was that of an emaciated colored man, aged 37, 72 inches (182.9 cm.) long and weighing 100 pounds (45.4 Kg.). There was a subicteric tinge to the sclerae. The supraclavicular and infraclavicular fossae were deep and the ribs prominent. On removing the breastplate, one saw in the thymic region six large, discrete, firm, decidedly brown nodes from 1.5 to 3.5 by 2 by 2 cm. On section, these

glands were deep brown with small grayish areas. The right border of the heart was 2 cm. to the right of the right sternal margin; the enlargement of the heart was due to a dilatation of the right ventricle and auricle, especially the latter. The heart weighed 290 Gm., and except for a pale, rather soft myocardium, showed no pathologic changes.

The posterior parts of both lungs were firm and woody. The anterior parts were distended with air, and the part near the apex presented large and small bullous enlargements; puncture of such a bullous body allowed the escape of air and caused the collapse of the bulla. Both apexes were occupied by firm masses of solid grayish and grayish-brown tissue in which pearly gray streaks could be seen. These masses extended down into the lower lobes, but were here broken up by small areas of air-containing lung tissue. Near the bases of the lungs, dark gray to black areas formed smaller, discrete nodules from 2 to 10 mm. in diameter, and often in the center of such a nodule could be seen a streak or speck of brown. In the apex of the lower lobe of the left lung there was an area made up of numerous grayish-white gelatinous patches ranging up to 6 mm. in diameter. Similar gelatinous areas were found in the right middle and the lowermost part of the right lower lobe (fig. 1).

The tracheobronchial lymph nodes were large, the largest being 5 by 3.5 by 3 cm. They were discrete, very hard and brown or grayish-brown, the brown being much more pronounced than in the lung tissue. In the centers of some of them were pinhead-sized grayish nodules.

The spleen weighed 240 Gm. and was firm. On the capsule were numerous pinhead-sized brown spots, like flakes of tobacco, slightly raised above the surface. The markings on the cut surface were indistinct, the pulp was firm and the trabeculae were thickened.

The liver weighed 1,900 Gm. The markings were distinctly seen, and the only abnormality was the coppery-brown hue of the organ.

Near the middle of the pancreas there was a single small, brown lymph node. The remaining organs showed nothing pathologic.

The anatomic diagnosis was: pulmonary siderosis of the black type; siderosis of the tracheobronchial, anterior mediastinal and peripancreatic lymph glands; tuberculous bronchopneumonia; tuberculosis of the tracheobronchial lymph glands; bullous emphysema of the lungs; chronic pleuritis; dilatation of the right auricle and ventricle; brown atrophy of the heart; chronic splenic tumor.

Microscopic Examination.—The lobular structure of the liver was well preserved. The cords of liver cells were of normal appearance and arrangement. Within the liver cells were golden brown granules of pigment, and occasionally these were clumped together; but they stained a deep orange with sudan III and were in all probability lipofuscin. Smaller dustlike granules of pigment giving the prussian blue reaction for iron were scattered diffusely through the cell. The sinusoids were dilated, but contained little blood. Into them protruded many cells which were prominent because they contained pigment. The cells were spindle-shaped, branched or stellate and adherent to the liver cords or slightly separated from them. Their nuclei were oval but obscured by the accumulation within the cytoplasm of tiny round particles of golden brown or deep brown pigment. Only occasionally could a cell be seen which was similar in all respects to those described but which contained no pigment. All of the granules stained deep blue with potassium ferrocyanide. Occasional Kupffer cells loaded with iron pigment were so large as to obstruct the lumen of the sinusoid. The portal areas were of normal size and were normal, except for the presence of a few large cells with round or oval nuclei which contained brown pigment giving the iron reaction. There was

nowhere any increase in connective tissue or lymphocytes. The pigment granules everywhere were round or oval; crystalloid or angular shapes were absent. Nor were there pigment granules outside of the cells. The capsule contained no pigment.

The malpighian corpuscles of the spleen were small. Their central arterioles were normal and were surrounded by a narrow zone of lymphocytes among which there were occasional large, oval, often branched cells containing tiny round pigment granules. The splenic sinuses were narrow, and were lined by low cells which showed no pigment even in the iron stain. Sometimes a large pigment-containing cell was visible within the lumen of a sinus. The splenic pulp was very cellular, made up of lymphocytes and macrophages, many of the latter containing fine, dustlike granules of brown pigment. Part of this pigment stained blue with potassium ferrocyanide, but some of it remained unstained. A single cell contained one or the other kind of pigment, never both. The amount of pigment giving the iron reaction was large; most of it was found at a distance from the malpighian corpuscles, while the greatest amount of pigment not giving the iron reaction was found in that part of the pulp immediately adjacent to the corpuscles. The connective tissue trabeculae were not thickened, but many of them contained large cells which were filled with round pigment granules giving the reaction for iron. There was no pigment free between the connective tissue fibers. The capsule was greatly thickened in small areas and contained a large amount of pigment all in the form of round, deep brown granules within cells and all giving the reaction for iron. The pigment-containing cells tended to occur in clumps.

The glomeruli of the kidney appeared normal. The tubules were slightly dilated; the lining epithelium stained poorly and was irregular and in places necrotic. The blood vessels appeared normal. Nowhere was pigment to be seen, and staining with potassium ferrocyanide revealed no iron.

The lymph nodes in the tracheobronchial, anterior mediastinal and peripancreatic regions all showed the same structure, except that there was less pigment in the last. The structure of the glands was made distinct by the dilatation of the marginal and the interfollicular lymph sinuses. These were lined by prominent endothelial cells which bulged into the lumen and were filled with golden brown pigment granules. Some of these endothelial cells were huge and widely distended by the pigment. The lumen of the sinuses was filled by pale cells, from about four to ten times as large as a small lymphocyte, with large, pale, oval, vesicular, eccentrically placed nuclei and with homogeneously pink cytoplasm. About one in every ten or fifteen of these cells contained pigment granules, usually only three or four round granules, sometimes many, so that the cell was sometimes filled. A few small lymphocytes were seen in the sinuses. Nowhere were there transition forms between lymphocytes and the large pale cells. All this pigment gave the prussian blue reaction for iron; and, in addition, many of the macrophages in the sinuses stained diffusely light blue, with the exception of the nuclei, as though the iron were in solution in the cytoplasm. The follicles were made up of a loose group of small lymphocytes between which there were many large round or irregularly branching cells packed with golden brown pigment. In the center of the follicles, these pigment-containing macrophages were close together and formed nodules. In the medulla there was a large amount of iron-containing pigment both within the sinuses and in the medullary cords.

The branches of the afferent lymph vessels outside of the capsule (fig. 2) were much distended; the lining endothelium was prominent and filled with iron pigment. Within the lumen were cells like those in the lymph sinuses, with about the same proportion of iron-containing cells. The branches of the efferent lymph

vessels in the hilus of the gland were similarly dilated, lined by pigment-containing endothelium and filled with iron-containing cells, but many of the latter were necrotic and there was much débris within the lumen.

Several of the lymph glands examined showed tubercles, for the most part small; only one large caseous area was found. Each tubercle consisted of a central necrotic area surrounded by macrophages filled with pigment. The necrotic areas, too, contained pigment, occasionally still within cells, more often free in the necrotic mass. The amount of pigment varied inversely with the size of the tubercle. Giant cells were few, but they contained clumps of iron pigment in the

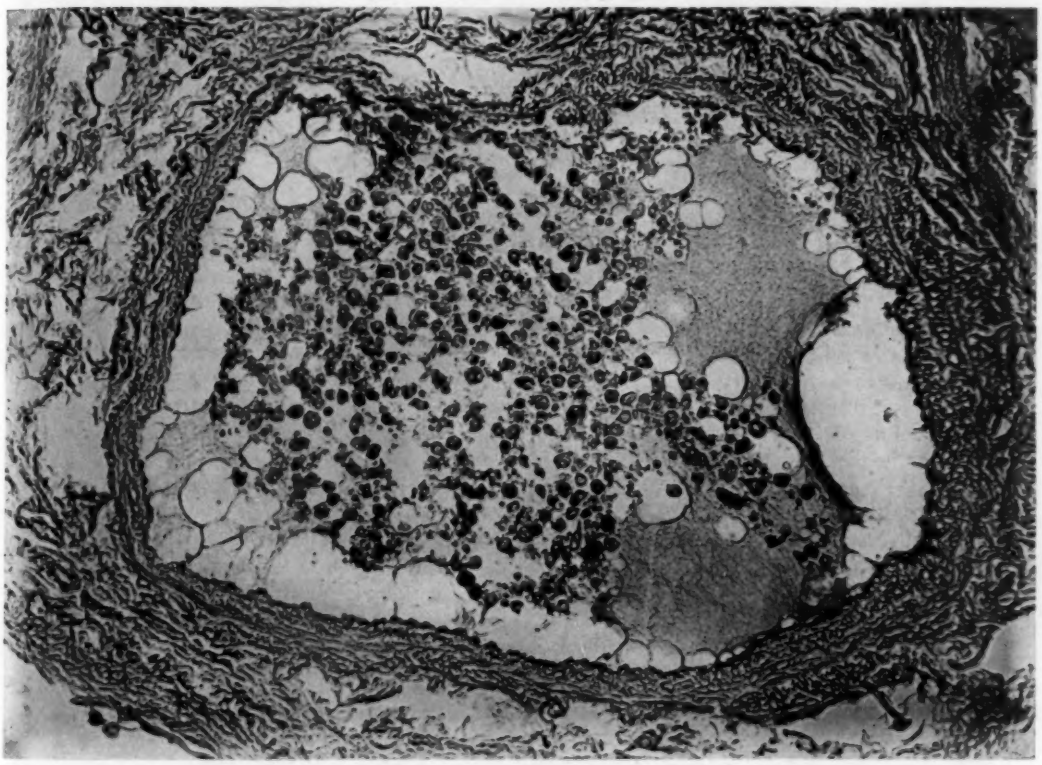

Fig. 2 (case 1).—An afferent lymph vessel at the periphery of a gland, treated with potassium ferrocyanide and hydrochloric acid followed by lithium carmine. All the black is iron. In addition, many of the cells are stained diffusely light blue.

center separated from the peripherally placed nuclei by a zone of iron-free cytoplasm. There was no attempt at encapsulation of the tubercles. The fat tissue around the lymph gland appeared normal, except that around the nuclei of the fat cells there were varying numbers of pigment granules which gave the iron reaction. The fat tissue in other regions of the body did not show the same phenomenon.

The pigmented, firm portion of the lungs was made up of dense strands of relatively acellular hyaline connective tissue, which formed an interlacing mesh-

work; in the interstices there were numerous large round cells filled with pigment, and a relatively small amount of extracellular pigment. The fibrocytes and the fibroblasts contained pigment granules close to the nuclei. The pigment was of three kinds: (1) black pigment, much of which was extracellular and tended to occur in clumps; (2) a deep brown pigment which did not give the prussian blue reaction for iron, was principally extracellular and was found in the denser parts of the tissue; (3) a deep brown pigment which gave the prussian blue reaction, was entirely intracellular and was present in the more cellular portions. In this thick tissue there were small groups of dilated and irregular alveoli, with the lining cells bulging out into the lumen, but only occasionally containing pigment. Within the lumen were numerous large round and oval cells with indistinct nuclei, the cytoplasm filled with round pigment granules. The largest of the cells were partially necrotic, and the pigment free in the lumen of the alveoli evidently came from the disintegration of these macrophages. Within the interalveolar septums there were many large cells filled with pigment. All of this pigment gave the prussian blue reaction. The smaller bronchi (fig. 3) were lined by tall columnar epithelium in which fine granules of brown pigment giving the reaction for iron were present between the nucleus and the free margin of the cell. This portion of the cell was large, stained poorly and could be seen in places to be partially pinched off; pieces of pigment-containing necrotic material were seen in the lumen of the bronchioles.

The dark nodules seen and felt in the lung had a characteristic structure. In the center there was a small branch of an artery. Around this, arranged in concentric fashion, were large pigment-filled cells. Fibroblasts, also arranged concentrically about the vessel, gave to the nodules the appearance of whorls of tissue about the central arteriole. All the pigment present gave the iron reaction, and all of it was intracellular. There was no pigment in the vascular endothelium or in the walls of the vessels.

The gray soft area in the lung was an area of tuberculous pneumonia with small foci of caseation, and with only occasional pigment granules.

Other areas of the lung showed scattered tubercles, some of which were close together and confluent, forming nodules of macroscopic size. These resembled closely the tubercles in the lymph glands; central necroses containing free iron pigment; a zone of macrophages loaded with pigment; many lymphocytes; few giant cells; almost no fibrosis. The tissue adjacent to the tubercles consisted of masses of large cells filled with iron pigment with no proliferation of connective tissue.

Bone-marrow and the gastro-intestinal canal were unfortunately not taken for microscopic study.

Chemical examination of the densest and blackest portion of the lung showed 8.9 per cent of the moist weight to be iron (computed as the oxide) and 12.5 per cent silicates.

CASE 2.—*History.*—A colored man, aged 38, entered the hospital on Oct. 26, 1928. He had worked in a mine in Alabama. How long he had worked in this or in similar mines is not known. For three years he had complained of weakness, shortness of breath and heart consciousness, and had lost 48 pounds (21.8 Kg.) in weight. For two years he had had a dry cough. Weakness was progressive. In the last four months he had had swelling of the feet, which disappeared at night; also nausea, which was most pronounced in the morning and was often accompanied by vomiting. Expectoration had been moderate; he had never had hemoptysis. For a year the patient had been hoarse. In his past there was nothing of

note, except that he had had pneumonia one year previous to entrance into the hospital; there was no history of tuberculosis in his family.

Physical Examination.—At the time of admission, the physical examination showed a poorly nourished colored man, who was apparently not acutely ill. He had wheezing breathing and a metallic cough which became worse on exertion. Examination of the chest showed prominent supraclavicular fossae with dimin-

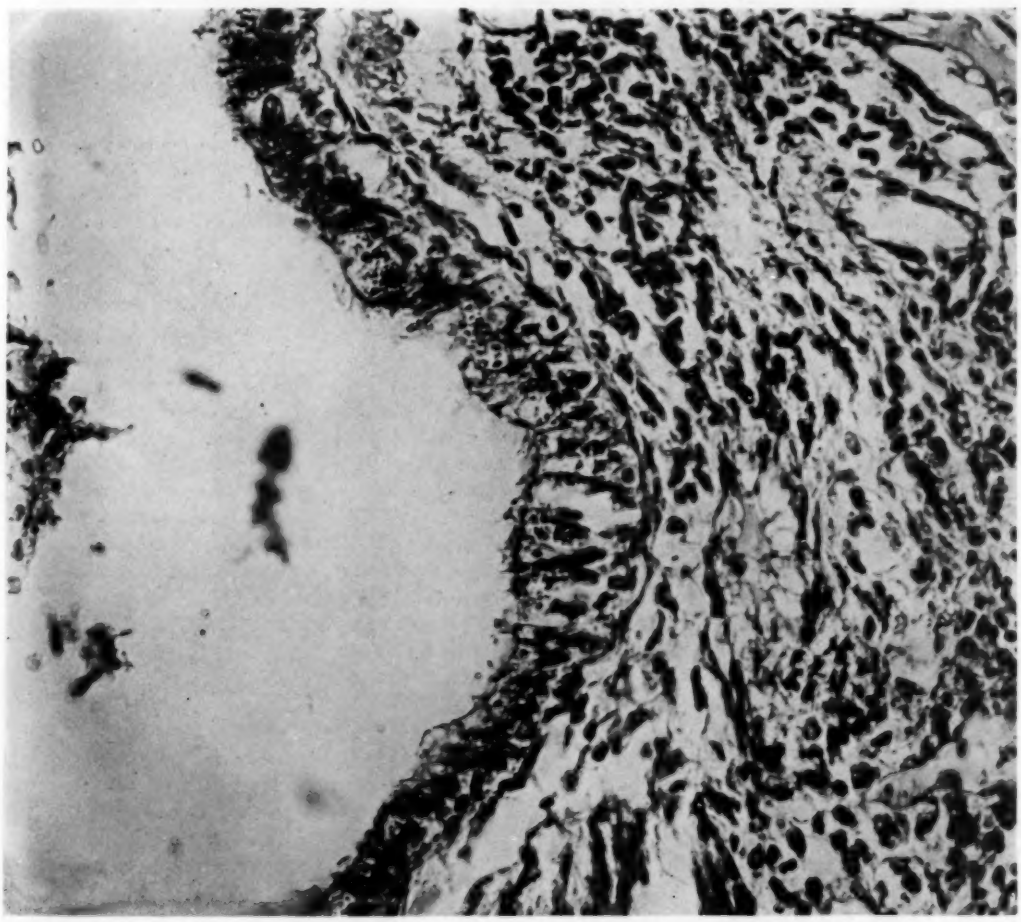

Fig. 3 (case 1).—A bronchiole with granules of pigment in the lining cells. At the extreme left are portions of desquamated epithelium containing pigment. This pigment gives the reaction for iron. Hemalum and eosin.

ished tactile fremitus and dulness on the right. The right apex and the entire left lung were dull on percussion. The breath sounds were increased on both sides, but there were no râles. The apex beat was displaced to 2 cm. to the left of the mammary line and was diffuse. The only abnormality in the heart sounds was a marked accentuation of the second pulmonic. His hemoglobin was 55 per cent (Sahli), and the red cell count 3,800,000. A moderate amount of albumin

and many casts were present in the urine. The results of the Wassermann and Kahn tests were negative. The temperature of the patient remained normal during his stay in the hospital, and his pulse rate varied between 90 and 116. A definite diagnosis was not made, but pulmonary tuberculosis and an aortic aneurysm were strongly considered. Roentgen examination showed increased density over the right upper lobe and almost the entire left lung, with some infiltrations in the right middle and lower lobes. The mediastinal structures were drawn toward the left. These observations were considered as evidences of advanced pulmonary tuberculosis.

The patient's condition remained about the same until November 6, when he suddenly began coughing a great deal, became very dyspneic and after a few hours died.

Necropsy.—Necropsy was performed about eight hours after death. The body was that of a fairly well nourished colored man, 38 years old, 68 inches (172.7 cm.) long and weighing 146 pounds (66.2 Kg.). The abdomen was slightly distended. On removing the breastplate, one found several large, firm, very brown lymph glands in the thymic region and slightly adherent to the under surface of the sternum. The left pleural cavity was nearly completely obliterated, and the lung was firmly adherent to the parietal pericardium. The right lung was moderately adherent posteriorly and near the apex. The pericardial sac contained about 150 cc. of clear, straw-colored fluid.

At the margin of the left apex there were large bullous enlargements which collapsed after puncture, with the escape of air under tension. The entire upper lobe and the apex of the lower lobe were consolidated and woody. A hard, deep reddish-brown mass occupied the entire upper lobe and seemed to be surrounded by a lighter capsule. The only structure to be made out in this mass was a whorl-like configuration (fig. 4). The upper part of the lower lobe was similarly consolidated, but there was no encapsulation, and the lower margin of the consolidated portion merged imperceptibly with the adjacent lung. In the rest of the lower lobe there were numerous hard brown nodules, from pinhead size to 3 or 5 mm. in diameter, more easily felt than seen. Their size and number decreased from above downward. The remainder of the lung tissue showed a prominent orange-brown reticulum. The right lung was of similar appearance. The entire upper lobe and about one third of the lower lobe were completely consolidated, but there was no definite encapsulation.

The tracheobronchial lymph nodes were all enlarged, brown, firm and discrete. Several of them, especially the larger ones, which measured 6 by 3 by 3 cm., showed areas of exactly the same appearance as the most consolidated parts of the lung; brown, firm masses, with a whorled gray structure faintly visible, surrounded by a definite capsule. Other glands showed prominent pinhead-sized nodules diffusely scattered through their substance. At the hilus of the right lung there was a single calcified lymph gland.

The liver weighed 1,800 Gm.; the capsule was smooth. The markings were prominent reddish areas on a yellowish background.

The spleen weighed 220 Gm. In the capsule were small nodular areas of brownish thickening. The parenchyma was soft, and contained much blood; the markings were indistinct.

The pancreas was firm and had a slightly brownish hue. The lobules were widely separated by fibrous tissue and fat. In the surrounding tissue were numerous brown lymph nodes, the largest 2 by 1 cm. Some were a homogeneous deep brown; others contained grayish, translucent areas.

Fig. 4 (case 2).—Pulmonary siderosis.

The kidneys, heart, brain, suprarenal glands and gastro-intestinal tract showed no pathologic changes.

The anatomic diagnosis was: pulmonary siderosis of the red variety; siderosis of the tracheobronchial, substernal and peripancreatic lymph glands; siderotic deposits in the capsule of the spleen; bilateral adhesive pleuritis; hydropericardium; atrophy of the pancreas.

Microscopic Examination.—The lobular structure of the liver was well preserved; the cords of liver cells were arranged in normal fashion; the blood spaces between them were dilated, but contained little blood. Many of the liver cells contained a few brownish granules which gave the prussian blue reaction for iron. The Kupffer cells were prominent; nearly all of them contained numerous golden brown granules, all of which gave the iron reaction. These cells also contained fat droplets; fat in fine droplets was found also within the liver cells. The portal areas were more prominent than normal; they contained accumulations of lymphocytes, but the greatest part of these areas was formed by connective tissue. In the latter there was a moderate quantity of deep brown pigment, some of it within small oval or spindle-shaped cells, most of it extracellular. None of this pigment gave the prussian blue reaction.

The malpighian corpuscles of the spleen were few in number, but of normal appearance. Among the lymphocytes there were large branched cells filled with brown pigment which gave the prussian blue reaction. The sinuses were dilated and contained much blood. Their endothelial lining cells were low cuboidal; they contained no pigment. In the pulp cords there were large round and oval cells containing round granules of iron pigment. Sometimes, instead of showing blue granules, the entire cell cytoplasm was stained blue. The trabeculae were slightly thickened and contained a few cells filled with iron pigment. The capsule was thickened and contained a moderate amount of pigment of two kinds: an intracellular pigment which gave the iron reaction, and an extracellular pigment which did not. The former was much greater in amount.

The kidneys were of normal appearance and contained no pigment.

Sections taken from the dense encapsulated mass in the upper lobe of the lung (fig. 5) showed only enormous masses of brown pigment contained within dense fibrous connective tissue which contained few nuclei. Small amounts of black pigment were also present. Only occasional granules of this pigment stained by the Perls method for ferric iron or by Nishimura's modification of the Turnbull reaction for ferrous iron. The capsule in this region was very thick, but much more cellular than the main mass. It, too, contained much pigment, but most of it was within large macrophages and stained deep blue by the Perls method.

Sections taken from the base (fig. 6) showed small nodules scattered through the parenchyma, which were most numerous near the capsule. Each nodule (fig. 7) showed a characteristic concentric layering of connective tissue about a small blood vessel; in the meshes of the connective tissue were numerous large cells distended by granules of dark brown and golden brown pigment. Nearly all of this pigment stained deep blue with potassium ferrocyanide. In the alveolar septums there were similar large cells containing iron pigment. In some areas, the alveoli were filled with large pigment-containing cells. The lining cells of the alveoli were never found to contain pigment.

The lymph glands in the tracheobronchial and anterior mesenteric regions showed two kinds of changes. One group, comprising especially the smaller glands and including the peripancreatic nodes, showed the same changes described for case 1: dilatation of afferent, marginal, interfollicular and efferent channels, with iron pigment in the lining endothelium and in the numerous macrophages

filling them, and iron pigment in numerous large pale cells within the follicles and especially in the medulla. The larger glands, however, had a different appearance: much or, in some glands, practically all of the lymphoid tissue had been replaced by large masses of connective tissue, relatively acellular but containing clumps of dark brown and golden brown pigment. Only a small portion of the pigment gave the reaction for iron. In glands in which some lymphoid tissue remained there were numerous pigment-containing cells, the pigment staining deep blue with potassium ferrocyanide.

Some of the glands showed tubercles; the mesenteric glands contained large areas of necrosis surrounded by tubercles, but no pigment. In the tracheobronchial and peripancreatic nodes, there were many tubercles made up of caseous

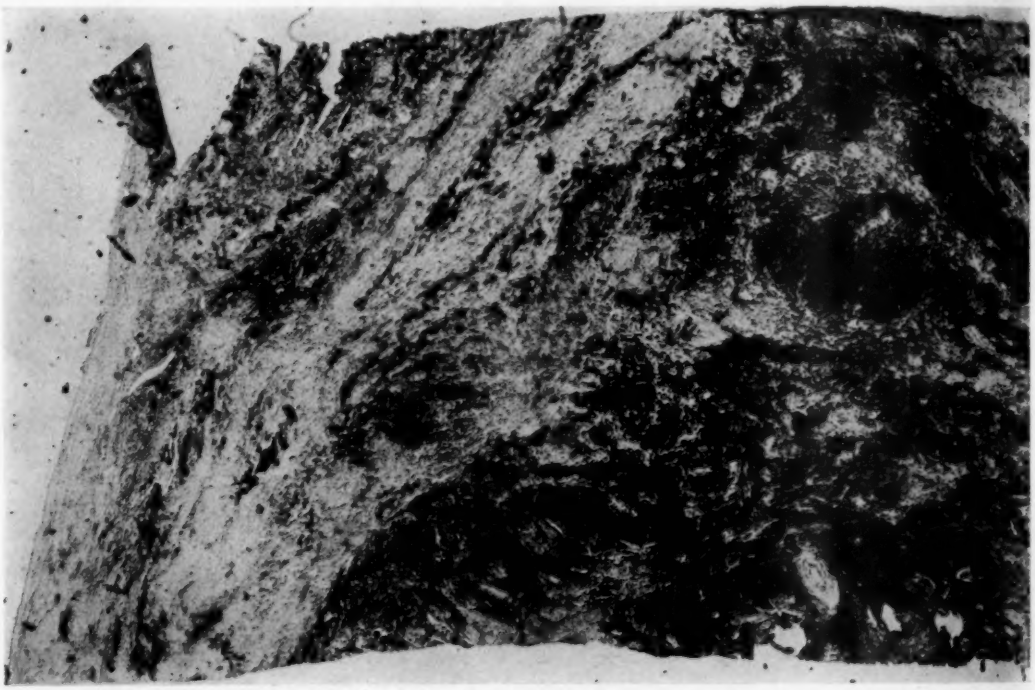

Fig. 5 (case 2).—The margin of the firm node in the apex of the lung. The pigment in the pleura gives the reaction for iron; that in the firm masses at the right does not.

centers containing pigment granules, surrounded by pigment-filled macrophages and showing one or two Langhans' giant cells. Many of the latter contained several granules of pigment. All of this pigment gave the reaction for iron. Staining of such sections by the Ziehl-Neelsen method revealed acid-fast bacilli within the tubercles.

Remnants of thymus tissue showed good differentiation of cortex and medulla. Hassall's bodies were partly calcified and contained fat. There was no iron pigment in the thymus.

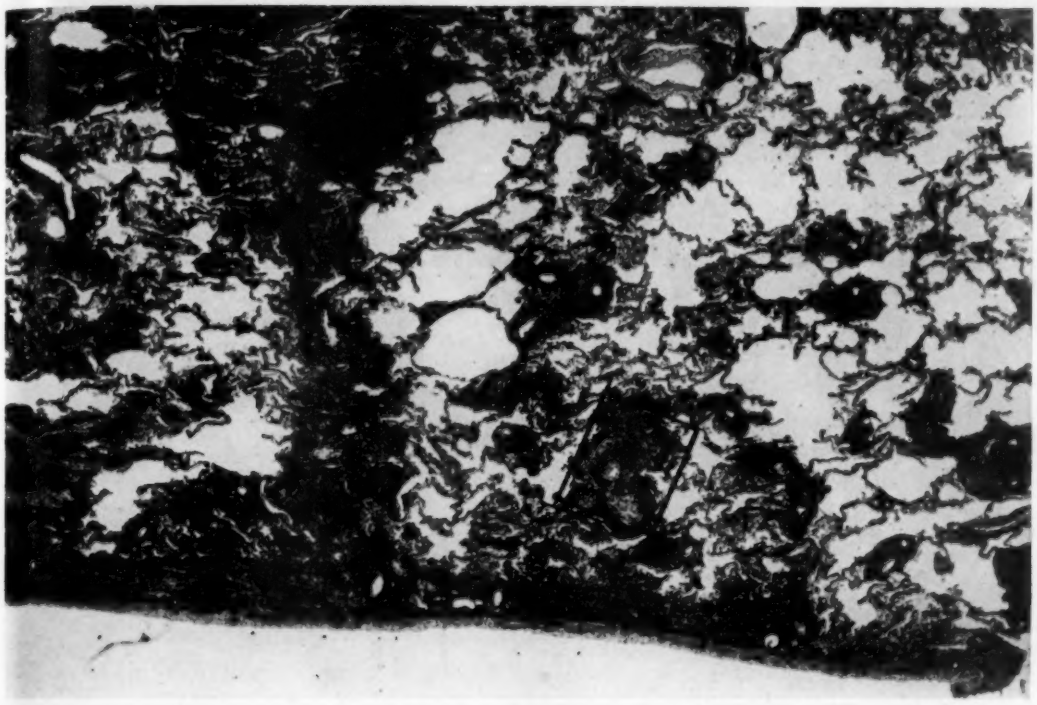

Fig. 6 (case 2).—Section from the base of the lung, seen under low power. Note the central arteriole in each nodule. The portion outlined by the rectangle is shown in figure 7. Hemalum and eosin.

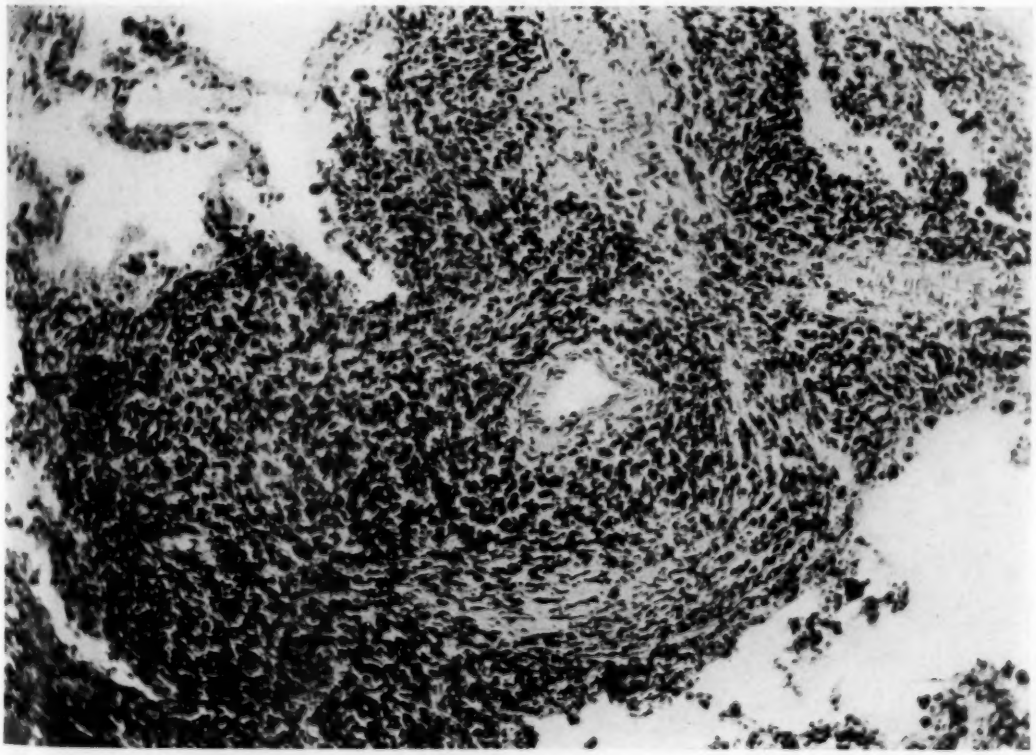

Fig. 7.—High power magnification of portion outlined by the rectangle in figure 6.

Chemical Examination.—Portions of tissue from the tumor-like area in the upper lobe of the lung yielded 7.96 per cent of iron (calculated as the oxide). Only slight traces of silicates were found and no other metals. Portions of the lung tissue dried in a paraffin oven were not attracted by a magnet, but putting such pieces of tissue for a moment in the Bunsen flame caused them to become so attracted. Heating the tissue slowly until all organic matter was removed left a rusty red powder which was attracted by a magnet.

COMMENT

These cases illustrate the reaction of the body to the presence of a large amount of iron and iron-ore introduced by inhalation. In many respects, siderosis is identical with other types of pneumonoconiosis. In all, the earliest lesions are small pigmented nodules which are perivascular and peribronchial accumulations of the dust. The number of such nodules is greatest in the upper parts of the lungs. As the nodules become larger, they acquire a firm fibrous capsule. In the apex, they are close together, and may become confluent and finally form a large tumor-like mass involving an entire apex. Oehmann [6] spoke of a granite hard upper lobe in one of his cases of silicosis. This massive infiltration has, however, been much more common in siderosis than in other types of pneumonoconiosis. If the migration of dust to the apexes is to be explained by a lymphatic spread, the greater solubility of iron may explain this greater frequency.

Enlargement of the lymph glands at the hilus occurs early and is a constant observation in pneumonoconiosis. Usually the glands are only moderately enlarged; only uncommonly have they been noted to approach the size found in the two cases herein reported. Klehmet [11] said that they may be seen in roentgen plates and that they may cause compression of the esophagus or trachea. In my second case, pressure of the glands on the recurrent laryngeal nerve caused hoarseness and a brassy cough, which led to the suspicion of an aortic aneurysm, a condition noted only once before (Klehmet [11]). Occasionally, lymph glands near the spleen or pancreas have been noted to contain the foreign matter (Klehmet). In my two cases, in which the lymph glands at the hilus of the lungs were very large, the peripancreatic glands were markedly involved. The peculiar retrosternal packet of brown glands, identical in these two cases, leading in the second to a diagnosis of siderosis immediately on removal of the breastplate at necropsy, has, so far as I have been able to find, never been noted.

The transportation of iron from its depots in the lung is interesting. Probably the most important mode of excretion is by the migration of iron-laden macrophages into the alveoli and their expectoration in the

11. Klehmet, M.: Zur Diagnose der Pneumokoniosen, Beitr. z. klin. d. Tuberk. **46**:153, 1921.

sputum. When large quantities of iron are present, the epithelium of the bronchioles may aid in the excretion (as in case 1), terminal cytoplasmic portions which contain the pigment being cast off. Thus if, after a careful taking of the occupational history, siderosis is suspected, iron may be found in the sputum by acidifying the latter with hydrochloric acid and adding potassium ferrocyanide, a deep blue color (prussian blue) indicating a positive reaction. In the case of a metal polisher, who, shortly after these two necropsies, entered the Research and Educational Hospital for a gastro-intestinal complaint, but who had a slight cough and expectoration, the aforementioned test applied to the sputum resulted at the end of a few minutes in the appearance in it of numerous fine deep blue flakes. Control tests on about fifty sputums from tuberculous patients showed no positive reactions. This test has been used successfully in iron mining districts by Klehmet,[11] Hoke [12] and others. Hoke noted that iron may be found in the sputum even five years after cessation of exposure. Hare [13] said that the sputum may be red in siderosis. Hoke [12] and Klehmet [11] described it as ochre-yellow. Zenker [1] found red specks in the sputum. Yet such sputum is not common, and in most cases only a chemical test will result in the discovery of the iron.

The iron which cannot be carried off in the sputum is in part removed from the lung by way of the lymphatic channels. It is probably for this reason (Tendeloo) that so much more iron is found in the upper lobes than elsewhere. Macrophages carry the pigment through the lymph vessels to the lymph glands. Some of these cells become necrotic in the course of their migration and the liberated pigment is taken up by the endothelium lining the lymph channels and the intraglandular sinuses. Some of the pigment is retained in the lymph glands; some passes through the gland and reaches the efferent lymph vessels. The finding of iron-containing macrophages in the efferent vessels of glands far removed from the hilus of the lung (anterior mediastinal and peripancreatic) is of importance in explaining what is to follow.

Black pigment, supposed to be coal dust, has occasionally been found in the spleen and less often in the liver; in anthracosis this is common. Riddell,[14] in a case of silicosis, found pigment in the center of miliary fibrotic areas in the liver and in fibrous nodules in the spleen. Langguth [5] found iron pigment in the spleen in a case of siderosis. It has

12. Hoke, E.: Die Eisenlunge, Med. Klin. **21**:766, 1925.

13. Hare, H. A., in Osler and McCrae: Modern Medicine, Philadelphia, Lea & Febiger, 1907, vol. 3, p. 752.

14. Riddell, A. R.: A Case of Silicosis with Autopsy, Canad. M. A. J. **15**:839, 1925.

been assumed, and the statement is to be found in most American and German textbooks of pathology, that the pigment which reaches the spleen and the liver gets there following the breaking of a disintegrating lymph gland into a blood vessel. Langguth gave the same explanation in his case of siderosis. Kaufmann [15] said that in severe cases of anthracosis the pigment may be transported directly from the lung to the blood. In these two cases a simpler explanation seems to be justified. The pigment reaches the blood stream through the lymph channels and the thoracic duct. For a long time, until the gland becomes fibrotic, there is no lymphatic blockade, but a continuous passage of pigment-laden macrophages through the lymph nodes, so that even in nodes far removed from the site of entrance of the dust such cells may still be found in the efferent vessels.

Severe cases of siderosis become, then, excellent means of studying the fate of inorganic iron injected into the blood stream of human beings. In rabbits, Polson [16] has recently studied the fate of such iron in experiments lasting as long as fourteen months. The earliest accumulations of iron were in the lungs. The tracheal lymph glands, but not the mesenteric, also contained iron. The liver at first contained only small amounts of iron in the Kupffer cells; the latter became enlarged, often forming giant cells. Later, the liver cells, too, contained fine granules of iron, but oftener gave a diffuse blue color with potassium ferrocyanide. In the last stages, iron was found only in "giant cells" at the periphery of the lobule. The spleen early contained much iron; later only small groups of iron phagocytes were found in the splenic pulp, which disintegrated, liberating free granules of iron. The kidneys contained no iron, except immediately after the injections, when emboli were found in the glomerular tufts. The pancreas contained no iron, unless foci of inflammation were present.

This corresponds closely in many respects with the observations in these two cases of siderosis. The differences are to be explained by the greater length of the human experiment. The ultimate fate of the pigment which cannot be excreted seems to be inclusion within dense connective tissue.

In addition to transportation there is a gradual transformation of the iron pigment. Some of the iron gives the prussian blue reaction; some of it does not. Of course, in case 1, it may be thought, and with good reason, that the nonreacting pigment is a silicate; but in the second case all the pigment has been shown by chemical analysis to be iron.

15. Kaufmann, E.: Pathology, English translation, Philadelphia, P. Blakiston's Son & Company, 1929, vol. 1, p. 421.

16. Polson, C. J.: The Fate of Colloidal Iron Administered Intravenously, J. Path. & Bact. **32**:247, 1929.

Yet in the dense parts of the upper lobes and the fibrotic lymph glands in even this second case most of the iron gave no typical reaction. Staub-Oetiker [17] noted that in areas of fibrosis in siderosis there was no reaction for iron, while in the periphery there was a strong reaction for iron. Unless the iron is included in a complex radical (as in a ferrocyanide), no inorganic form is known which will resist hydrochloric acid (as in the Perls method for iron) without dissociation to give a form which will react with a ferrocyanide or ferricyanide; no such complex inorganic iron compounds are known in the animal body. The probability is, then, that the nonreacting iron is strongly combined with organic compounds, in a form as resistant to acid, as is, for instance, hemoglobin.

It is to be remembered that in these two cases the pigment which gave the reaction for iron was almost entirely intracellular (except in necrotic regions); the nonreacting pigment was almost entirely extracellular. To give the reaction, the pigment must be soluble. It seems reasonable to conclude, therefore, that the iron which is in transport is in soluble form. As soon as it becomes firmly combined with protein, it remains stationary, surrounded by dense connective tissue.

It is clear, too, why siderosis more than other types of pneumonoconiosis should be accompanied by a widespread distribution of the pigment. In the first case in which there was much more silicon than iron in the lung only the more soluble iron was present in the liver and spleen (all the pigment in these organs gave the prussian blue reaction).

The distribution of the transportable iron is within cells of the reticulo-endothelial system; the wandering macrophages, the Kupffer cells of the liver, the reticulum cells of the spleen and lymph nodes and the lining endothelium of the lymphatic vessels and lymph sinuses. The littoral cells lining the splenic sinuses contained no pigment. Nowhere was pigment found in the endothelium of blood vessels. The thymus, lying embedded in a mass of siderotic lymph glands, contained no iron. The large cells making up the tubercles contained iron, except in the large caseous areas, in which iron was found only as free granules in the center. In neither case were there many giant cells in the tubercles, but most of those present contained granules of iron in their centers.

It is worthy of note that in spite of the large amounts of circulating inorganic iron there was anemia in both cases. Even the hyperglobulia often accompanying chronic pulmonary fibrosis, which has been noted in other types of pneumonoconiosis (Hoke [12]), was absent in these cases. It is even possible that the excess of iron may have acted as a poison to cause the anemia. In the second case, the slight amount of

17. Staub-Oetiker, H.: Die Pneumokoniose der Metallschleifer, Deutsches Arch. f. klin. Med. **119**:469, 1916.

fibrotic tuberculosis of the lymph glands could not be responsible for the low red cell count. It is to be recalled that Carleton [8] found early death from a toxic influence in guinea-pigs exposed to massive doses of iron dust.

SUMMARY

Two cases of pulmonary siderosis are reported: one in which the dust was metallic iron, produced the black variety of siderosis and ended in a florid tuberculous bronchopneumonia, and one in which the dust was iron ore, the siderosis of the red variety and the concomitant tuberculosis of the fibrotic type and limited to the lymph glands.

In both cases there was a continuous attempt at excretion of the iron by macrophages which carried it into the alveoli and thence into the sputum, by excretion through the bronchiolar mucosa or by transference to the lymph nodes. In the last event, the pigment was either deposited in the gland or was carried through the gland and reached the blood stream probably by way of the thoracic duct. Having reached the blood stream, the iron was deposited in the cells of the reticuloendothelial system.

In addition to transportation, there was gradual transformation of the iron. Only the soluble iron could be transported and was found intracellularly. In the black variety, in which more silicon than iron was present in the lung, only the more soluble iron found its way into the blood stream. Insoluble iron was found extracellularly in dense fibrous tissue.

Where the accumulations of iron were greatest, the amounts present were 8.9 and 7.9 per cent of the moist weight of the lungs.

Chemical examination of the sputum for iron may be a great aid in the clinical recognition of siderosis.

THE GIANT CELLS OF BENIGN GIANT CELL TUMORS OF BONE*

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Many different views have been advanced in an attempt to establish the origin of the typical giant cells that are found in benign giant cell tumors of bone. Between the years 1890 and 1900, this was a much discussed topic. A review of the literature reveals the fact that the number of ideas on the subject nearly equalled the number of authors who wrote on the question. From 1900 until the present, the literature contains no accounts of a special investigation of this subject, except for one article by Mallory [1] in 1911.

Many cases of benign giant cell tumors of bone have been reported in the interim, and in each report a statement is made regarding the origin of the giant cells, but such statements can not be considered to be of any particular value because they are largely echos of statements made in preceding articles. Thus King and Towne [2] in a recent report followed Mallory,[1] Goforth [3] followed Virchow,[4] etc.

Kolodny [5] threw an interesting side light on the present situation when he quoted what he termed "the theory of histogenesis of the giant cell in vogue today."

Before entering on an investigation of any subject, the ideas previously advanced should be known. In going back through the literature, I ran across the most varied concepts. Virchow [4] and Rindfleisch began the discussion by asserting that the giant cells are hypertrophied bone cells set free by absorption of the bone matrix and are identical with osteoblasts. Borst [6] agreed with this view and went further to say that since these cells are from the bone, the entire tumor is of bony origin.

Ziegler [7] considered the giant cells as being formed by the process of indirect segmentation of the nuclei of osteoclasts.

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1. Mallory, F. B.: Giant Cell Sarcoma, J. M. Research **24**:463, 1911.

2. King, N. J., and Towne, G. S.: Giant Cell Tumor of the Patella, Arch. Surg. **18**:892 (March) 1929.

3. Goforth: Giant Cell Tumor of Bone, S. Clin. North America **7**:299, 1927.

4. Virchow, R.: Die Krankhaften Geschwülste, Berlin, A. Hirschwald, 1864, vol. 2, p. 335.

5. Kolodny, A.: Bone Sarcoma, Surg. Gynec. Obst. (suppl. 1-2) **44**:1, 1927.

6. Borst, N.: Das Verhalten des Endothelium bei der acuten und chronischen Entzündung, Verhandl. d. phys.-med. Gesellsch. zu Wurzburg **31**:1, 1897.

7. Ziegler, E.: Lehrbuch der allgemeinen und speciellen pathologischen Anatomie für Aerzte und Studirende, ed. 8, Jena, G. Fischer, 1895, vol. 2, p. 447.

Klebs [8] stated that the giant cells are large, rapidly growing osteoblasts which develop from decomposing bone cells and enlarge through mitotic division of the nuclei.

Manz [9] claimed two possible modes of origin for the giant cells: (1) formation by rapidly proliferating elements through multiple segmentation of nuclei and (2) in degenerating tumor tissue, from confluence of protoplasm of damaged cells.

Several authors were of the opinion that they are derived from endothelium of angioblastic tissue. Wegner and Malassez [10] agreed. Stroebe [11] stated that "blood-vessels and giant cells stand in intimate relation. Fine capillaries are seen entering and piercing the giant cells, perhaps without any genetic relation being present. Sometimes the lumen of blood-vessels is seen sunken inside the giant cell body. One often sees protoplasmic processes in a vessel lumen, or the latter more or less fills the body of the giant cell." He concluded, therefore, that "giant cells develop from endothelium."

Lubarsch [12] noticed identical conditions and is in entire agreement with Stroebe.[11] His belief was that the giant cells are "abortive vascular sprouts."

Ritter [13] made similar observations. He pointed out the presence of what other authors termed "vacuoles" inside the giant cells. He said, "That we have to deal with vacuoles which are present in movable cells is hardly believable. We can not exclude that in many cases we have to deal with a lumen which was already formed from vascular buds, because in a number of cases we have seen in such vacuoles red blood cells." He also drew an analogy by tracing the cells in Howship's lacunae to proliferating vascular endothelium.

So it is seen that, by 1900, various ideas had been advanced. Giant cells were thought to originate from bone cells, osteoblasts, osteoclasts, decomposing bone tissue, aggregate masses of stroma cells, confluence of protoplasm of decayed cells and from endothelium or angioblastic tissue.

In 1911, Mallory [1] advanced the idea that these giant cells are formed at first by agglutination of the large mononuclear leukocytes of the blood; and later as a result of retrograde processes. He drew attention to the fact that foreign bodies of any kind draw the large mononuclear leuko-

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8. Klebs, E.: Die allgemeine Pathologie, Jena, G. Fischer, 1889, vol. 2, p. 743.

9. Manz: Ueber Riesenzellensarkom der weiblichen Brustdrüse, Beitr. z. klin. Chir. **13**:66, 1895.

10. Wegner and Malassez, L.: Arch. de physiol. norm. et path., 1878.

11. Stroebe, H.: Beitr. z. path. Anat. u. z. allg. Path. **7**:341, 1890.

12. Lubarsch, O.: Reisenzellensarkoma, Ergebn. d. allg. Path. u. path. Anat. **1, 2**:365, 1895.

13. Ritter, C.: Die Epulis und ihr Reisenzellen, Deutsche Ztschr. f. Chir. **54**:1, 1899-1900.

cytes from the blood to the part affected. These cells then fuse, forming the foreign body giant cell. On boring a hole into the femur of a rabbit and leaving the bone dust, he observed the formation of these giant cells about the dust particles. From this experiment, he assumed that the giant cells of benign giant cell tumors of bone were similarly produced, although he made no investigations of the giant cells in such bony tumors. From the experiments on rabbits, he concluded that all giant cells of this type are formed in the same manner and signify only erosion and disintegration of bone substance.

In a recent article on the interrelation of giant cell tumors of bone and osteitis fibrosa, Geschickter and Copeland [14] stated that the giant cells are always associated with fresh blood and new blood vessels. They concluded, however, that the giant cells are accumulations of the round cells of the stroma, since they believed a histologic similarity can be seen in the nuclei.

Today all these various concepts still stand, and little attempt has been made to sift the evidence, and to confirm or disprove any of them. Ewing [15] in his book, "Neoplastic Diseases," sidestepped the issue by saying that "the origin of the giant cells is attributed both to bone cells and proliferating angioblastic cells."

OBSERVATIONS

In order to obtain further information at first hand, I made an examination of a series of eleven specimens of benign giant cell tumors of bone which had been collected in this department during the past twelve years. Of five of these specimens, paraffin blocks were found, which enabled us to prepare additional microscopic slides. The remaining six are surgical specimens of which only one microscopic slide was sent to the department for the purpose of examination. The evidence that I present in this paper represents the accumulated experience obtained by a careful examination of all of the eleven specimens. The photomicrographic tracings that accompany the article represent pictures from eight of the specimens; the remaining three were found to be unsuitable for photographic work, although the conditions found in them are similar. High power photomicrographs were taken, and tracings made from them. This procedure was resorted to because in this way the details could be much better shown and the essentials to be brought out could be more clearly depicted.

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14. Geschickter, C. F., and Copeland, M. M.: Osteitis Fibrosa and Giant Cell Tumor, Arch. Surg. **19**:1 (Aug.) 1929.

15. Ewing, J.: Neoplastic Diseases, ed. 2, Philadelphia, W. B. Saunders Company, 1922, p. 280.

The cells under discussion are the typical, large, multinuclear cells found in benign giant cell tumors of bone. They vary greatly in shape and size and are opaque, acidophil cells containing small, oval, uniformly shaped nuclei, which are grouped in the central parts of the protoplasm. They resemble the so-called "foreign body giant cell." It is found that these cells are much larger than would be suspected by observing them in a single microscopic slide. By cutting serial sections it has been possible to identify the same cell in three and sometimes four consecutive sections. Thus it is shown that cell processes and connections that are not apparent in one section can be found when other sections through the same cells are examined.

The giant cells are found most abundantly in actively growing tumors and in areas rich in blood vessels. This fact has been noted by many authors, and may be considered as definitely established. This in itself suggests that there must be a connection between blood-vascular elements and the giant cells.

In previous articles, the claim has been made that the accumulations of blood found in these tumors are usually due to hemorrhage. This idea has been refuted many times, and my observations agree with the opinion of those who hold that this is not so. I find that in most cases the blood does not lie in undefined pools, as one would expect if hemorrhage had occurred, but is present in narrow preformed channels, which are close together in some areas and farther apart in others. Moreover, one does not always find the amount of pigment and of fibrous tissue that should result from the organization of numerous old hemorrhages. The tumors are evidently extremely vascular, and most of the blood lies in definite, large capillary channels.

In all specimens, giant cells were found which formed part of the lining of these capillary channels in such a way that living, circulating blood elements were found in immediate contact with them. It is especially important to note that there never is a layer of endothelium between the capillary lumen and the giant cells. Instances of these facts are shown in tracings *A*, *B*, *C* and *D* in figure 1. In each of these pictures, giant cells are shown forming portions of the walls of capillaries. The capillary channels are all definitely outlined, and the nuclei of the endothelial lining definitely shown. In every instance, the endothelium stops where the giant cell forms the wall of the vascular channel, so that the latter lies in immediate contact with the circulating blood.

Having established these facts and knowing that endothelium is the normal lining of blood channels, I attempted to ascertain if there actually is a connection between the endothelium and the giant cells. Evidence that this is true was found in every specimen. I have been able to show instances of giant cells developing in direct continuity with the blood

vessel endothelium. The giant cell protoplasm extends into the endothelial wall at both sides and the cell, per se, thus lines directly the blood channel, and on each side of the cell the normal endothelium carries on the definite vessel outline (fig. 1).

Stroebe, in the article referred to earlier in this paper, recounted the observation that fine capillary spaces are seen entering and piercing the

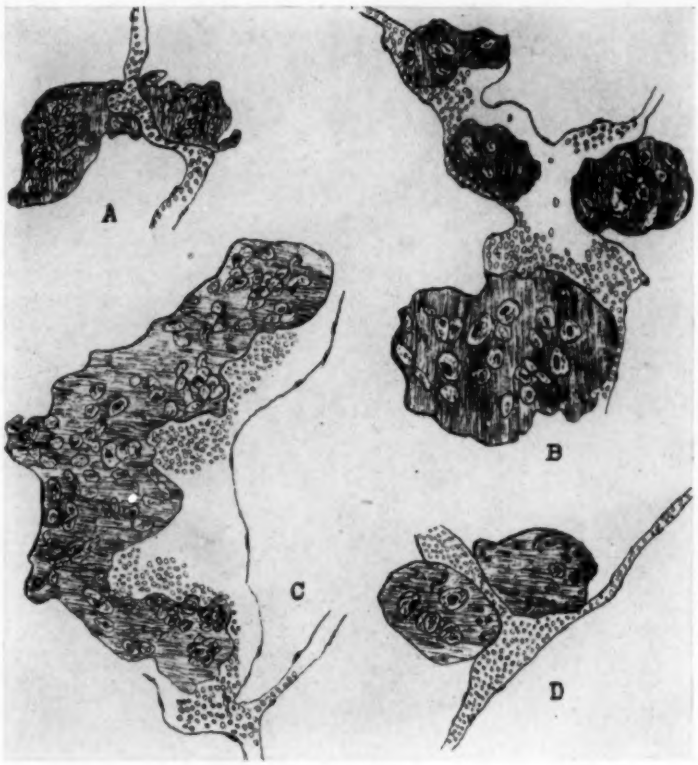

Fig. 1.—Blood vessels, the walls of which are partially formed by giant cells. Note particularly that there is no endothelium interposed between the vessel lumen and the giant cells. *A*, two giant cells forming portions of the walls of a capillary. *B*, four giant cells of varied size forming a large portion of the walls of a blood channel. The small cell that appears to lie within the vessel is forming part of the posterior wall of the channel, the remaining three line the walls. *C*, one large giant cell forming the lining of a blood channel. Blood fills the channel and lies in immediate contact with the cell. *D*, a capillary dividing two giant cells. The latter form the walls of the vessel.

giant cells. I can confirm this observation. In some instances, in which by chance a giant cell has been cut in exactly the plane necessary, it can be seen that the cell has been hollowed out from the vessel's side so that

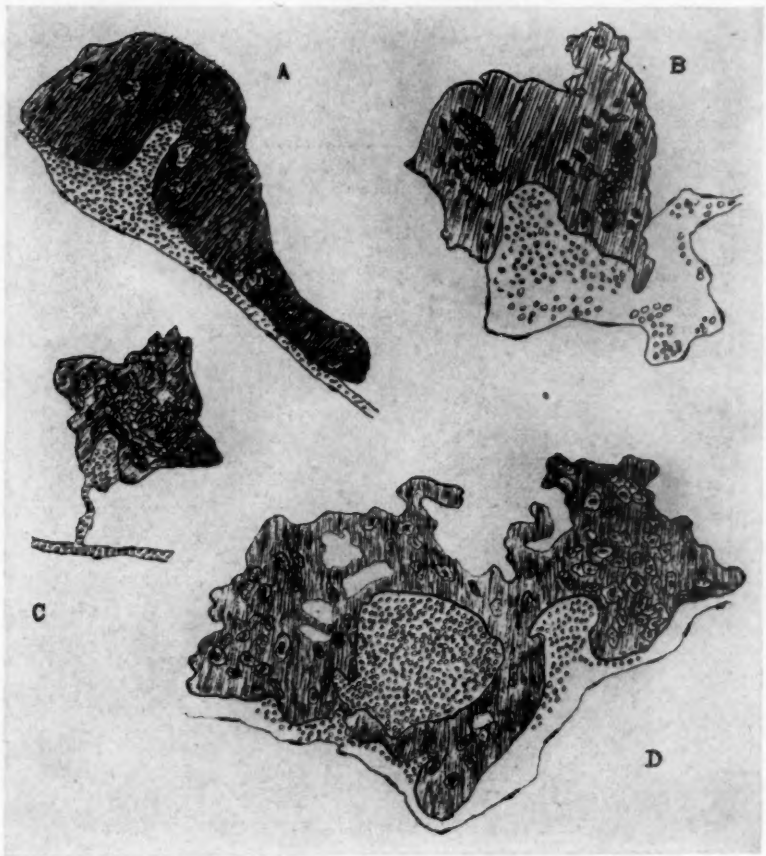

Fig. 2.—Giant cells lying in the walls of blood vessels; hollowing out of the giant cells has begun and blood is seen in the new channels. Note particularly that no endothelium is interposed between the blood elements and the giant cells. *A*, a giant cell forming a portion of the lining of the side of a vessel. The hollowing out of the cell has begun from the blood vessel side, and this hollowed portion contains blood elements. *B*, a giant cell is being hollowed out. Blood elements are seen in the hollowed portion of the cell. *C*, a giant cell formed at the end of a capillary. The cell is partially hollowed out from the capillary's end. Blood is seen inside the hollowed portion of the cell. *D*, a large giant cell forming a portion of the wall of a capillary. The hollowing out process has occurred in two places. Direct connection between the new vessels within the giant cell and the formed capillary can be seen. Four smaller channels running in the opposite direction contain no blood and appear as "holes."

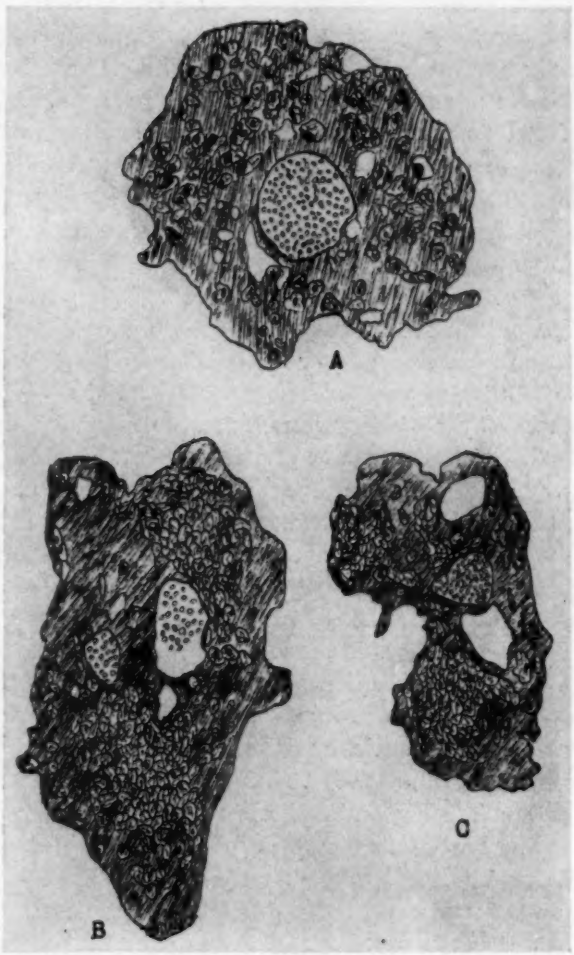

Fig. 3.—Giant cells in the bodies of which new blood channels are seen. Some of these channels are empty and appear as "holes," the "vacuoles" or "phagocytosed fatty droplets" of some authors; others are filled with blood. Note that the walls of these channels are formed directly and entirely by the giant cell. *A*, a large giant cell, hollowed out and cut so as to show a cross-section of an intracellular capillary which is filled with blood. *B*, a large giant cell, hollowed out and cut so as to show cross-sections of two intracellular capillaries which contain blood. *C*, a large giant cell containing three large intracellular capillaries, one of which is filled with blood. The remaining two are identical in structure with the former, but are empty.

blood channels are formed, communicating with the vessel and running into the giant cell. Thus new blood channels are formed. Figure 2, tracings *A*, *B*, *C* and *D*, depicts instances in which the hollowing out process has occurred. Blood is seen to be present in the capillaries and extends directly into the hollowed out portions of the giant cells. Here again the intimate relation of endothelium and giant cells is shown, as well as the fact that the normal endothelial lining of the vascular channels is lacking in the portions where the giant cells form the walls of the capillaries.

Should a cell that contains such a blood channel be cut in the opposite direction, a cross-section of the newly formed capillary would show within the protoplasmic body of the giant cell. The picture would be that of a giant cell in the body of which there is a round opening of capillary size. Practically all authors on the subject have noted this point and, since there seemed to be no other explanation of these occurrences, have labeled these holes "vacuoles," or attributed them to phagocytosed fatty droplets. Ritter was certainly correct when he stated that vacuoles in vigorous, growing cells are hard to imagine as a possibility. If these are bits of phagocytosed fat, they should stain readily with the differential fat strains, which is not the case. There must therefore be another explanation. I believe that it can be shown that these holes are new blood channels. Blood has been found in them in many places. In adjacent cells and sometimes in the same cell, these new blood channels, identical in every way, can be observed, some containing blood and others empty. I believe that this definitely proves that these spaces are the lumen of new blood channels. Figure 3, tracings *A*, *B* and *C*, show giant cells containing within their bodies cross-sections of these channels filled with blood. Tracing *C* also shows two empty blood channels that lie parallel to and are identical with the one that contains blood. These empty capillaries are the spaces that have frequently been taken for "vacuoles" or "phagocytosed fatty droplets" by some authors. Here again the blood is shown to be in intimate contact with the giant cells, no endothelium being interposed.

This completes the proof of the endothelial origin of the giant cells. Confirmation of these observations should be readily obtained by any one who carefully examines the giant cells in these tumors microscopically in serial sections.

SUMMARY

On microscopic examination of giant cells from eleven specimens of benign giant cell tumors of bone, I have found that giant cells are most numerous where the vascular tissue is most abundant; that giant cells form a portion of the lining of blood-vascular spaces; that there is no

break in continuity between early giant cells and the endothelial lining of the vascular spaces; that the giant cells lie in immediate contact with living blood elements without the interposition of an endothelial lining; that excavations or hollows in the giant cells communicate directly with the lumen of blood vessels; that the "holes" seen frequently in the body of a giant cell are in reality the lumen of newly formed blood-vessels, many of them being filled with blood.

These observations show that the giant cells of benign giant cell tumors of bone arise from the endothelium of the blood capillaries.

CONGENITAL ATRESIA OF THE TRICUSPID ORIFICE *

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CHICAGO

Congenital atresia of the tricuspid orifice of the heart is a rare cardiac anomaly. Rauchfuss,[1] in 1878, thought that only five of the sixteen reports of tricuspid atresia which he found in the literature concerned true developmental defects, while the others described lesions which had probably resulted from fetal endocarditis. Kühne,[2] in 1906, reported two cases in which atresia of the tricuspid orifice was not associated with other grave cardiac deformities, and she reviewed the descriptions of six similar instances already on record. She classified these lesions as simple congenital atresia of the tricuspid orifice. Kühne's classification was later supported by Wieland [3] who described an instance of atresia of the tricuspid orifice in 1914 and called attention to a report made by Sieveking [4] in 1854. Huebschmann [5] reported two instances of tricuspid atresia in 1921, but only the first of these was a simple atresia belonging to Kühne's group. Additional reports were made by Mönckeberg [6] in 1924 and by Rihl, Terplan and Weiss [7] in 1929.

Recently a patient with congenital atresia of the tricuspid orifice was observed in the pediatric service of Dr. Isaac A. Abt at St. Luke's Hospital.

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* Submitted for publication, April 12, 1930.

* From the Henry Baird Favill Laboratory and Pediatric Service of St. Luke's Hospital.

1. Rauchfuss, C.: Die angeborenen Entwickelungsfehler und die Fötalkrankheiten des Herzens und der grossen Gefässe, Handbuch der Kinderkrankheiten, herausgegeben von Gerhardt, Tubingen, 1878, vol. 4, part 1, p. 99.

2. Kühne, M.: Ueber zwei Fälle kongenitaler Atresie des Ostium venosum dextrum, Jahrb. f. Kinderh. **63**:235, 1906.

3. Wieland, E.: Zur Klinik und Morphologie der angeborenen Tricuspidalatresie, Jahrb. f. Kinderh. **79**:320, 1914.

4. Sieveking: Congenital Malformation of the Heart: Absence of the Right Atrioventricular Orifice, Patulous Foramen Ovale, Defective Interventricular Septum, Tr. Path. Soc. London **5**:97, 1854.

5. Huebschmann, P.: Zwei Fälle von seltener Herzmissbildung, Verhandl. d. deutsch. path. Gesellsch. **18**:174, 1921.

6. Mönckeberg, J. G.: Die Missbildungen des Herzens, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, J. Springer, 1924, vol. 2, p. 1.

7. Rihl, J.; Terplan, K., and Weiss, F.: Ueber einen Fall von Agenesie der Trikuspidalklappe, Med. Klin. **25**:1543, 1929.

A white male infant (J. E.), aged 8½ months, was brought to the hospital because of attacks of cyanosis noticed by the mother since the baby was 2½ months of age. At first the attacks occurred only when the child was restless or feeding, but later there was an almost continuous cyanosis of the hands and feet. At the onset of the attacks, the child had an acute left suppurative otitis media, and the discharge from the left ear did not stop entirely. The infant was undernourished. His birth weight was 9 pounds and 5 ounces (595.3 Gm.) and he had been breast fed for only three months. There was no history of cardiac disease in the family, and both parents and a brother and sister were in good health. All three children had been delivered by cesarean section.

During the physical examination the child became extremely cyanotic when crying or moving about, and when it was quiet the lips, hands and feet were

Fig. 1.—The probe in the right ventricle of the heart is inserted into the defect of the interventricular septum.

blue. There were many coarse râles in the chest posteriorly, especially at the bases of the lungs. A loud systolic murmur was heard over the entire precordium and in the left axilla, with a region of maximum intensity in the second and third left rib interspaces near the sternum. The borders of the heart were determined with some difficulty, but were apparently within normal limits. The liver was palpable about 2 cm. below the costal margin.

In the hospital the dietary difficulties were overcome. The child was much improved, when the exudate from the left ear suddenly increased. The infant became dyspneic and more cyanotic and coughed. There was a moderate fever, râles were heard in the entire chest and the child died three weeks after entering the hospital. Clinically, the cause of death was bronchopneumonia and congenital heart disease.

Postmortem examination was made twenty-two hours after death. The body was that of a poorly nourished, white male infant, 67 cm. long and weighing 11 pounds (5 Kg.). The mucous membranes of the mouth and lips were markedly cyanotic. The pleura of both lungs was covered with a viscid purulent exudate, and the pericardium was moderately enlarged. Within the pericardium was a small amount of clear yellow fluid, and the lining was unchanged. The right auricle was huge, and the moderately enlarged ventricular portion of the heart consisted almost entirely of the left ventricle. The diameter of the root of the aorta was 1.5 cm., while that of the pulmonary artery was 0.8 cm. When the auricles were opened dorsally the lumen of the right was three or four times as large as that of the left. The myocardium of the right auricle had a thickness of 3 mm. as compared with a thickness of 1 mm. on the left side. The patent foramen ovale in the upper portion of the interauricular septum was 0.7 cm. in

Fig. 2.—A pitlike depression in the base of the right auricle marks the site of the obliterated tricuspid valve; to the left of the depression are defects of the lower portion of the interauricular septum.

diameter. In the base of the right auricle was a pitlike depression 1 mm. deep, about which was a slight fibrous tissue thickening of the endocardium, but there was no trace of a tricuspid orifice. A short distance to the left of the depression was a circular place in the interauricular septum 0.7 cm. in diameter, partially closed by a coarsely fenestrated membrane the openings in which varied from 1 to 3 mm. in diameter. The mitral orifice admitted the tip of one finger. The right ventricle was small and was found below the dilated right auricular appendage lying in a plane parallel to the coronary sulcus. The lumen, measured from the attachment of the pulmonic leaflets to the apex, was 2.5 cm. long, 0.7 cm. wide, and 0.3 cm. deep. The lining was smooth and pale red. In the septal wall, 1.5 cm. from the attachment of the pulmonic leaflets, there was an opening 0.3 cm. in diameter through which a small probe could be passed into the left ventricle.

The endocardium at the margin of the opening was slightly thickened with fibrous tissue. Above the opening the wall of the right ventricle was smooth, while below the myocardium was coarsely trabeculated. There were only two leaflets of the pulmonic semilunar valve, and these leaflets were unchanged. The circumference of the pulmonic ring was 1.5 cm. Nowhere in the ventricle was there a vestige of the tricuspid orifice or valve leaflets. The myocardium of the right ventricle was 2 mm. thick. The lining of the left ventricle was smooth and light red, and there were no changes of the leaflets of the mitral or aortic semilunar valves. The orifices of the coronary arteries were widely patent and there was no abnormality of the origin or distribution of these vessels. The distance from the mitral ring to the apex of the ventricle was 4 cm. and that from the attachment of the leaflets of the aortic semilunar valve to the apex was 4 cm. The circumference of the aortic ring was 3.5 cm. and that of the mitral ring 5.5 cm. The lining of the left and right auricles and auricular appendages was smooth. A probe passed into the opening of the septal wall of the right ventricle entered the left ventricle below the aortic ring beneath the commissure between the right and posterior aortic cusps. There was therefore a defect in the upper portion of the interventricular septum about 3 mm. in diameter. The thickness of the myocardium of the left ventricle varied from 0.7 to 1 cm. The ductus arteriosus permitted the passage of a fine probe.

There was bilateral hypostatic bronchopneumonia, but in none of the other tissues of the chest and abdomen were there any noteworthy changes. The important items in the anatomic diagnosis, therefore, were congenital atresia of the tricuspid valve; patent foramen ovale; persistent interauricular and interventricular foramina; hypoplasia of the right ventricle of the heart; marked hypertrophy of the myocardium of the right auricle and left ventricle of the heart; bicuspid pulmonic semilunar valve, and acute bilateral bronchopneumonia.

The heart described closely resembled those classified by Kühne as simple or isolated atresias of the tricuspid orifice. The characteristic observations in these hearts are a patent foramen ovale, an obliterated tricuspid orifice and a defect of the interventricular septum. The blood passes from the right auricle through the defects in the interauricular septum to the left auricle, where it mixes with the aerated blood from the lungs and then continues through the mitral valve into the left ventricle. A part of the blood is then forced through the interventricular septal defect into the right ventricle and pulmonary artery, while the remainder is emptied into the aorta.

COMMENT

The etiology of congenital atresia of the tricuspid valve is related so intimately to the development of the septums of the heart that a brief review of their embryology is in order. Mönckeberg, basing his discussion of the development of the heart on an extensive study of the literature dealing with this subject, stated that the heart of the human embryo at the end of the third week has three definite divisions: the sinus venosus, the atrium and the bulboventricular loop. The bilaterally dilated atrium, which lies anterior to the sinus venosus, is continuous below with the left ventricular descending limb of the bulboventricular

loop, while the right ascending bulbar limb gradually bends medianward and then passes upward anterior to the atrium. The lateral outpouchings of the atrium extend anteriorly and partially surround the bulbus arteriosus. The heart chambers at this stage of development are unpaired and consist of the lumen of the sinus venosus, which opens into the right dilatation of the atrium, and the lumen of the atrium, which in turn communicates through the single atrioventricular canal with the chamber of the primitive ventricle of the heart. At the end of the third week a vertical fold or septum primum grows downward and forward into the lumen of the atrium from the upper posterior wall. The free margin of the fold is concave and encloses an opening, the foramen primum. The anterior and posterior prolongations of the septum extend to the middle of the anterior and posterior margins of the ostium of the atrioventricular canal. As the septum approaches the atrioventricular orifice, there appear thickenings of the endocardium in the anterior and posterior walls of the canal. These endocardial cushions fuse with each other in the midline when the free margin of the interatrial septum touches them, dividing the single atrioventricular channel into the right and left atrioventricular canals. The endocardial cushions fuse with the lower margin of the septum, obliterating the interatrial foramen, but before this fusion is complete a defect occurs in the posterior upper portion of the septum primum and gradually extends forward. This is the foramen ovale. A second sickle-shaped septum, or septum secundum, now forms in the anterior wall of the right atrium to the right of the septum primum. The ends of the sickle extend posteriorly and converge to form a ring. The septum secundum then fuses with the right side of the septum primum, and only that portion of the septum primum seen from the right atrium through the ring in the septum secundum remains uncovered. The margins of the opening in the septum secundum are the margins of the fossa ovalis, and the uncovered portion of the septum primum is the valve of the foramen ovale. The interventricular septum grows from the knee of the bulboventricular loop and extends upward and anteriorly. Its free margin is concave, and the anterior prolongation of the septum extends to the lower margin of the bulbus arteriosus, while the posterior prolongation extends to the fused endocardial cushions of the atrioventricular canal. The foramen thus left between the ventricles is closed relatively late in the embryologic development of the heart by the septum of the bulbus arteriosus and the intermediate septum of His. In the second month of fetal life two spiral endocardial ridges arise in the truncus and bulbus arteriosus, which fuse across the midline from above downward, dividing the truncus and bulbus into an aortic and a pulmonic portion. This septum grows toward the ventricles with its concave margin directed downward and posteriorly. Its anterior process fuses

with the anterior arm of the interventricular septum, while the posterior process extends to the fused endocardial cushions. As the septum enlarges, it fuses with the intermediate septum of His, posteriorly closing the interventricular foramen. According to His, the intermediate septum originates in the spina vestibuli which is a connective tissue thickening in the lower posterior portion of the right atrium that projects into the atrioventricular canal below the margin of the septum primum and fuses with the endocardial cushions. The spina vestibuli fuses with the free margin of the posterior prolongation of the interventricular septum, and finally unites anteriorly with the interbulbar septum. At the end of the eighth week, the heart has four separate chambers.

Atresia of the tricuspid valve may follow inflammation of the endocardium or may result from a true defect in development. Rauchfuss stated that at least five cases of atresia that he found reported in the literature followed fetal endocarditis, for there were definite traces of inflammation. Vierordt [8] suggested that endocarditis is more likely to occur in the congenitally deformed than in the normal heart, and that in many cases tricuspid atresias thought to be of inflammatory origin are in reality true congenital lesions with a superimposed endocarditis.

Three explanations of the cause of congenital tricuspid atresia have been advanced. Rauchfuss proposed that an overgrowth and fusion of the endocardial cushions to the right of the interatrial septum produced an obliteration of the valve. Since this fusion takes place before the formation of valve leaflets, the usual absence of the vestiges of the tricuspid valve is explained. The position of the obliterated tricuspid orifice either cannot be determined or is marked by a slight depression in the base of the right auricle. Vierordt suggested that the obliteration of the right atrioventricular orifice resulted from an unequal division of the primitive atrium by a septum deviated too far to the right. As the septum fuses with the endocardial cushions, it seals over the right atrioventricular orifice and allows the development of only the left atrioventricular canal. This explanation was later supported by Wieland and Mönckeberg. Kühne stated that in early fetal life the septum primum is directed toward the right margin of the single atrioventricular orifice, but that, as the atrioventricular canal normally shifts from left to right, the free margin of the septum finally meets the lips of the orifice squarely in the middle, giving the impulse to fusion of the endocardial cushions. This results in two equally large canals. When the shift to the right fails to occur or is only partially complete, there follows an atresia or stenosis of the tricuspid valve.

The defects of the lower portion of the interauricular septum in the instance of tricuspid atresia described in this paper were probably rem-

8. Vierordt, H.: Primäre Fehler am Ostium venosum dextrum, in Nothnagel, Hermann: Specielle Pathologie und Therapie, Viena, 1901, vol. 15, part 2, p. 197.

nants of the foramen primum. They were found just to the left of the endocardial depression thought to mark the site of the obliterated tricuspid valve. Mönckeberg believed that this anomaly is caused by an unequal division of the primitive atrium by a septum deviated too far to the right. As the lower margin of the septum cannot fuse completely with the endocardial cushions, a persistent foramen primum remains. The opening in the upper portion of the interventricular septum may also be a true developmental defect. This is suggested by the associated observations of a bicuspid pulmonic semilunar valve and a moderate stenosis of the pulmonary artery. Mönckeberg found that defects of the membranous portion of the interventricular septum are frequently present in hearts with a bicuspid pulmonic semilunar valve. An unequal division of the bulbus arteriosus by the interbulbar septum, with narrowing of the pulmonic channel, may prevent the development of the anlage of one of the pulmonic valve leaflets. However, as the obliteration of the tricuspid orifice occurs somewhere in the fourth week of embryonic life while the interventricular foramen is not closed until the seventh or eighth week, it is possible that the mechanical force of the blood flowing from the left to the right ventricles has prevented the interbulbar septum from uniting with the interventricular and intermediate septums.

The other changes in the heart can also be explained on the basis of the disturbed circulation. Thus, hypertrophy of the right auricle is due to the increased amount of work necessary to force the blood through the foramen ovale into the left auricle. This current of blood from the right to the left auricle also keeps the foramen ovale open. The left ventricle hypertrophies because it must supply not only the systemic but the pulmonic circulation, while the right ventricle is merely an atrophic appendage of the left. Kühne believed that a deviation of the interventricular septum to the right corresponding to the right deviation of the interauricular septum explained the extreme aplasia of the right ventricle. Huebschmann thought that in the hearts which he described the small right ventricular chamber was a conus pulmonalis rather than a true ventricle.

SUMMARY

The postmortem examination of an infant 8½ months of age disclosed congenital atresia of the tricuspid orifice of the heart associated with defects of the interauricular septum, hypoplasia of the right ventricle and a subaortic defect of the interventricular septum.

The most important symptom of this lesion clinically was cyanosis, increased by slight exertion, with an associated loud systolic murmur of the heart heard over the entire precordium.

The developmental defects of the heart were similar to those which Kühne and Wieland described as simple tricuspid atresias, of which about thirteen cases have been recorded.

THE INFECTION OF RABBITS WITH THE ANTHRAX BACILLUS BY WAY OF THE TRACHEA

STUDIES ON THE DEFENSIVE AND METABOLIC APPARATUS OF THE LUNGS *

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Experiments with the intratracheal injection of vital dyes and oils [1] have shown that these substances are largely disposed of in the lungs by large mononuclear phagocytic cells that are normally present in the pulmonary septums and also alongside the wall of the air sacs. If one is to judge from these "infections" with oils and dyes, which ought to be regarded as "model infections," the lungs possess a defensive mechanism of their own which in all probability also takes care of pathogenic micro-organisms that have made their way into these organs from without.

The purpose of the experiments to be reported was, then, to study the pulmonary reaction in animals infected with a pathogenic organism by way of the trachea.

The anthrax bacillus was chosen because the disease caused in rabbits by this micro-organism is characterized by a long incubation period as compared with the rather short subsequent illness. Indeed, contrary to what has been taught until recent times, this bacillus disappears almost instantaneously from the circulation even when introduced directly into the blood. Apparently, the micro-organism remains "immured" for a certain length of time within the tissues, being released into the blood at the terminal period of the illness. In fact, a rabbit infected with this gram-positive micro-organism remains in apparently good health until a short period preceding his death, at which time his blood appears to be flooded with the bacillus.

It was accordingly presumed that this protracted "symbiosis" between the cells and the micro-organism might enable one to observe the tissue reaction to the invader accurately and in great detail. It also was thought that the observation would be facilitated by the large size of the

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* From the Surgical Laboratory of the Peter Bent Brigham Hospital.

1. Fried, B. M.: The Origin of the Histiocytes (Macrophages) in the Lungs, Arch. Path. **3**:751 (May) 1927; The Defensive and Metabolic Apparatus of the Lungs: The Lungs and the Macrophage System, ibid. **6**:1008 (Dec.) 1928.

batonet and its tinctorial properties. And finally, since this organism is infallibly fatal to laboratory animals, it was believed that the obtained results would not be subject to ambiguous interpretations.

MATERIAL AND TECHNIC

The experiments were performed on full grown rabbits.

Two highly virulent strains of *Bacillus anthracis,* 168 and 325, secured from the State Laboratory of the City of New York, were used. The bacillus was grown on plain agar slants, and a twenty-four hour growth was finely emulsified in physiologic solution of sodium chloride.

Since *Bacillus anthracis,* when injected into laboratory animals, even in infinitesimal amount, is infallibly fatal, the experiments were conducted so as to introduce the organism into the pulmonary parenchyma without bringing it into contact with the extrapulmonary tissues. This was done in the following way: A sterile needle was inserted between the lower rings into the lumen of the exposed trachea. A syringe containing the infectious material was then attached to the needle, and the material was slowly injected into the bronchial tree. The syringe was then detached and the needle washed out with a newly attached syringe containing a physiologic solution of sodium chloride. After withdrawal of the needle, the puncture wound was cauterized.

EXPERIMENTS

The experiments can be divided into two series: (1) a series in which the rabbits receiving the injection of the anthrax bacillus by way of the trachea were left alive for observation, and (2) a series in which the animals were killed at intervals of from five minutes to three weeks after the intratracheal infection. The experiments were invariably accompanied by "controls" infected subcutaneously with one half, one third or less of the amount used in the intratracheal injections.

First Series of Experiments.—Twenty-one rabbits were used in this series. One cubic centimeter of an emulsion containing from 1,000,000 to 500,000,000 anthrax bacilli was injected into the bronchopulmonary tree of every rabbit in the manner indicated.

Three of the twenty-one animals died within two or three days as a result of a faulty technic; the characteristic gelatinous edema was present in the area of inoculation. Three rabbits died because insufficient precautions were taken to avoid local contamination; they were regarded, therefore, as controls. The remaining fifteen animals in which the described technic was strictly adhered to survived the heavy intratracheal injections.

The following are protocols of two experiments that are characteristic of the whole series:

Protocol 22: On Nov. 20, 1928, rabbits 125 and 126, weighing each about 2.5 Kg., were inoculated via the trachea with 300,000,000 anthrax bacilli, emulsified in 1 cc. of a physiologic solution of sodium chloride. The animals were not anesthetized, and the customary precautions were taken to avoid local contamination.

The animals remained symptom-free, and when killed by an air embolus three weeks later, the examination of their lungs revealed no pathologic changes.

Control: Rabbit 127 of the same breed, color and weight as rabbits 125 and 126 received subcutaneously about 50,000 bacilli; the animal was found dead in its cage about seventy hours after the infection, with typical anthrax.

Protocol 43: Rabbits 151 and 152, weighing each about 2 Kg., received into the lungs by way of the trachea about 500,000,000 anthrax bacilli emulsified in 1 cc. of a physiologic solution of sodium chloride. When killed eighteen days later, they showed no disease.

Control: Rabbit 153 that received simultaneously and without any local precautions an intratracheal injection of one twentieth of the amount given to rabbits 151 and 152 died fifty-two hours later with typical anthrax.

The experiments showed that manifold fatal doses of the anthrax bacillus can be introduced into the lungs of the rabbit with impunity when the micro-organism is brought directly in contact with the pulmonary tissue.

That the lungs represent an unfavorable pathway for infection with pathogenic micro-organisms of other kinds has been demonstrated on many occasions. In animals infected by way of the trachea septicemia has failed to develop in most instances, and no local lesions have been disclosed.

Of particular interest are the experiments with the production of pneumonia in animals. *Pneumococcus pneumoniae* is regarded as being the organism par excellence for the infection of the lungs, yet no observer has ever been able to produce pneumonia in the rabbit, the guinea-pig or even the mouse in instances in which the trachea was chosen as a vehicle for the coccus.

The harmlessness of the anthrax bacillus to small laboratory animals when the germ is introduced into the lung in the manner described has been stressed recently by Besredka,[2] who produced evidences to show that in the guinea-pig and in the rabbit the skin is the single organ that is susceptible to infection with *Bacillus anthracis*.

From the experiments here reported it will be seen that the bacillus is innocuous in the rabbit when introduced by way of the uninjured respiratory tract.

The mechanism of the pulmonary resistance will be analyzed in the section to follow.

Second Series of Experiments.—In the second series of experiments, the animals were killed by an air embolus at forty-one different intervals after the intratracheal infection, the intervals ranging from three minutes to thirty days. These experiments, too, were accompanied by "controls" infected subcutaneously with one twenty-fifth or one fiftieth of the amount used in the intratracheal injections. The freshly removed lungs

2. Besredka, A.: Vaccination par voie cutanée. Charbon: Cuti-infection, cuti-vaccination, cuti-immunité, Ann. de l'Inst. Pasteur **35**:421, 1921.

were fixed in a solution of formaldehyde and in Zenker's fluid. The staining method recently described by Lillie [3] for gram-positive bacilli furnished results comparable with those of the customary Gram-Weigert stain.

A résumé of the histologic changes found in the lungs follows:

When the lungs were examined under the microscope about five minutes after the infection took place, the micro-organism was found singly or in small groups

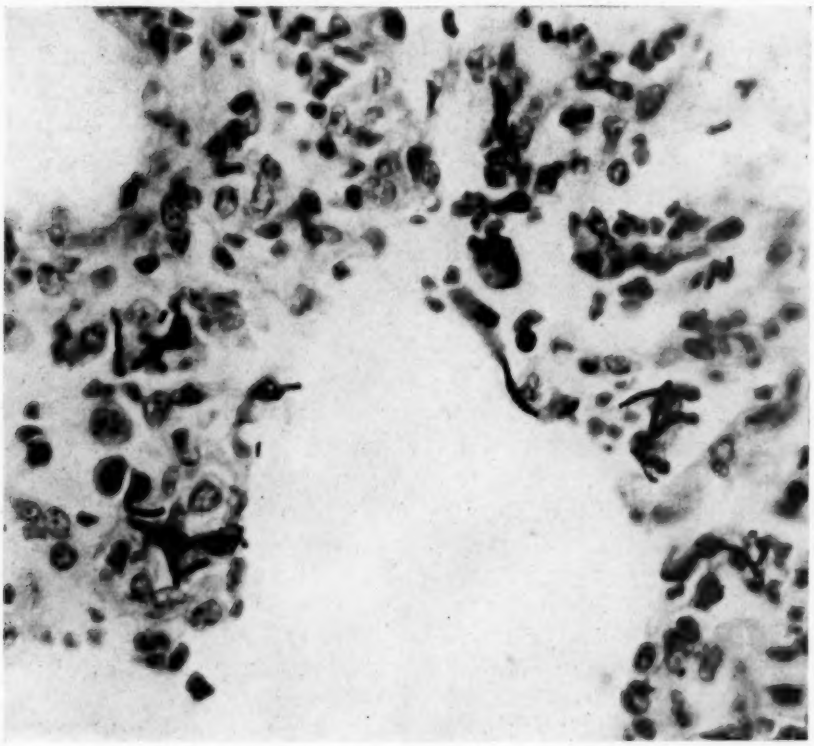

Fig. 1.—Proliferation of cells of the pulmonary septums and phagocytosis of anthrax bacilli by these cells; Gram-Weigert stain; × 600. The animal was killed about forty-five minutes after the intratracheal infection.

or as long whiplike filaments lying in the lumen of the alveoli adjacent to the septums. The bacillus was perfectly stained, showing no apparent morphologic changes. The blood vessels showed no congestion, and no migration of cellular elements from the blood could be noticed. However, already at this period the pulmonary tissue was striking in that it showed marked swelling of the cells lining the alveolar wall and of those present in the septums. These cells were

3. Lillie, R. D.: The Gram Stain: A Quick Method for Staining Gram-Positive Organisms in the Tissues, Arch. Path. **5**:828 (May) 1928.

each the size of a large lymphocyte and had each an oval or bean-shaped eccentric nucleus with a cytoplasm that showed large and small vacuoles. A large number of these cells lay free in the alveolar lumen and contained one or many agglutinated bacilli. In many places, the gram-positive micro-organism was outside of but intimately close to the cell; apparently the cell had not yet succeeded in "engulfing" it (fig. 1).

In the following minutes, that is ten, fifteen, twenty and up to about one hour, the cellular reaction was found to be increasing in intensity, as evidenced by multiplication and by swelling of the cells lining the septums, a great number

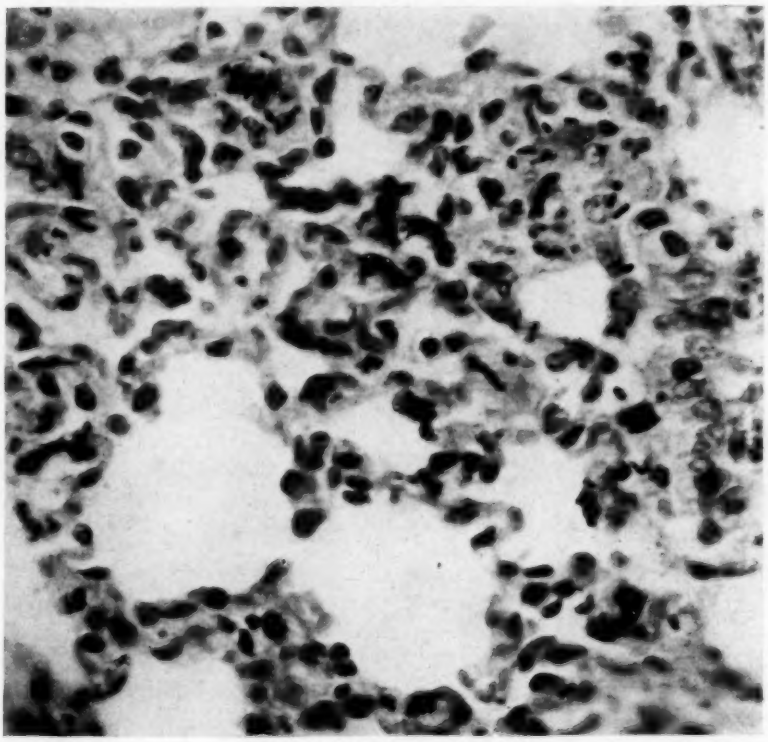

Fig. 2.—Proliferation of the cells of the pulmonary septums and phagocytosis of anthrax bacilli, which are agglutinated and fragmented. In some cells, the bacillus is seen as minute black (gram-positive) "dots"; Gram-Weigert stain; × 600. The animal was killed about two hours after the intratracheal infection.

of which, having separated from the wall, had migrated into the air sacs. The phagocytosis of the bacillus by these cells had largely increased, and the micro-organism itself showed swelling with hazy outlines, and often "crumbling" into small particles. The whiplike threads noted in the first few minutes had disappeared (fig. 2).

The "exudate" was moderate, and there was no striking outpouring of cells. The bacilli apparently did not multiply in the lung. On the contrary, with every added ten or fifteen minute interval, they appeared to be scantier, and those still

present showed disfiguration and fragmentation. After periods of two or three hours, the elongated, "slim" anthrax bacillus could be seen mostly as intracellular minute "dots" stained with the Gram stain. Within the next two or three hours, even these remnants of the pathogenic organism had entirely disappeared (fig. 3). The cellular exudate by this time had largely disappeared, but the cells alongside the wall of the air sac were still swollen with large hyperchromatic nuclei, and the entire lung appeared under the microscope to show a marked increase in "nuclei."

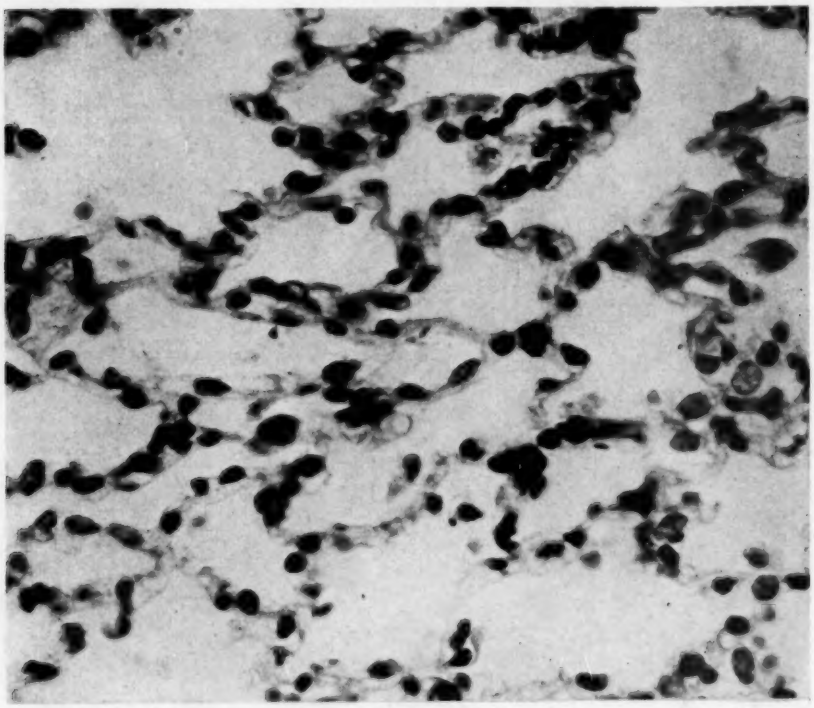

Fig. 3.—Lung of a rabbit infected with the anthrax bacillus via the trachea; Gram-Weigert stain; × 600. The animal was killed about seven hours after the infection took place. The bacillus has entirely disappeared from the lung. Bacillary remnants, seen as gram-positive "dots," can still be found in the cytoplasm of the free ameboid macrophages. The cellular exudate is insignificant, but the cells alongside the septums are still "swollen," and are increased in number.

The anthrax bacillus had thus disappeared from the lung within a period of from six to eight hours, and the pulmonary tissue at this period showed no particular changes.

The lymph nodes showed no changes. The blood from every killed animal was cultivated invariably with negative results. The liver, the spleen and the bone-marrow showed no histologic change and no gram-positive bacilli. These viscera were not cultivated or inoculated into animals for the purpose of detecting the possible presence of the anthrax bacillus.

INTERPRETATION OF EXPERIMENTS

It may be seen that: (1) a micro-organism of even such high pathogenicity as the anthrax bacillus causes no disease in the animal when introduced directly into the lungs, and (2) the micro-organism is destroyed in the lungs with great rapidity by local cellular elements found within the septums and alongside the wall of the air sacs. From this study it also appears that the reaction of the lung to a virtual infection with a highly pathogenic bacillus resembles closely that of the "model infection" with dyes and oils described in previous reports.[1]

Following my earlier studies,[1] the defensive apparatus of the lung has been the object of new investigations by numerous workers. The discussion has centered around: (1) the lining of the air sacs, that is, whether it represents a continuous or a discontinuous layer of cells; (2) the rôle of the cells "lining" the alveolar wall in inflammatory and congestive processes of the lung, and (3) the nature of these cells, i. e., whether they are endodermal or mesodermal.

These questions, which have been discussed at length in previous publications,[1] will be briefly considered here:

With regard to the lining of the air sacs, there is at the present time a prevalence of opinion that the walls of the alveoli are lined, not by a syncytial row of cells, but by scattered groups of cells, which are conspicuous at the bifurcation of the capillaries, similar to the Kupffer cells in the liver. The alveolar wall is therefore virtually "naked."

It is interesting that the fact of the "nakedness" of the air sacs was apparently known to some older observers. Thus in studying the absorbing power of the mucous membrane of different organs, Claude Bernard [4] found that toxins and poisons are absorbed by way of the alveolar surface as rapidly as by way of the blood stream. He noticed that curare placed on the mucosa of the bronchi caused no harm to the animal, but that when this alkaloid was "pushed" into the alveoli it killed the animal as rapidly as if it had been injected into the circulation. Claude Bernard attributed this phenomenon to the "absence d'un épithélium protecteur â la surface des vésicules pulmonaires." In a recent investigation, the French pathologist, Policard,[5] stated: "The respiratory surface of the lung ought to be compared to an open wound (à une plaie vive)." This is of importance in that the pulmonary respiration is not performed through the intermediary of the "respiratory epithelium," as has been thought by physiologists, but the alveolar air apparently comes in direct contact with the mesenchyme.

4. Bernard, Claude: Leçons sur les effets des substances toxiques et médicamenteuses, Paris, Baillière, Tindall & Cox, 1857.

5. Policard, A.: Les nouvelles idées sur la disposition de la surface respiratoire, Presse méd. **37**:1243 (Oct. 5) 1929.

Likewise, the notion that the "readily available" alveolar phagocytes are not imported but are locally produced has come to be accepted by Aschoff (Seeman [6]), by Gardner and Smith [7] and by Policard.[5] Whereas, however, Gardner and Smith have traced the origin of the pulmonary phagocyte to the connective tissue of the septums, entirely disregarding the activity of the "alveolar epithelium," the other authors mentioned are in complete accord with me that the "alveolar epithelium" is par excellence the progenitor of the free alveolar ameboid macrophage.

There remains to be considered the nature of the "alveolar epithelium."

Seeman,[6] in a series of recent observations inspired by Aschoff, found, as I did, that in pathologic circumstances the "alveolar epithelium" proliferates with an amazing promptness, that it separates from the alveolar wall, forming the intra-alveolar exudate, that both the fixed ("lining" the septum) and the sessile cells (exudate) are phagocytic par excellence. He maintained nevertheless that the bronchiolar and the alveolar cells are endodermal, because they display similar appearances when impregnated with silver nitrate. He did not discuss the striking differences between the "sedentary" bronchiolar cell and its "restless" wandering polymorphic neighbor, the alveolar wall cell, except the phagocytosis. Concerning this matter he said:

"The outstanding phagocytic activity of the 'alveolar epithelium' should not surprise us if we remember that occasionally the liver, kidney, adrenal and testicular cells are strongly phagocytic."

Those familiar with Aschoff's contributions to the problem of the reticulo-endothelial system will remember that this opinion expressed by Seeman is but a part of a statement previously made by his teacher, Aschoff. In quoting Ribbert and Rössle to the effect that the hepatic and renal epithelial cells are phagocytic, Aschoff [8] added, however:

. . . Das gelegentlich alle möglichen Zellen gröbere Fremdkörper in sich aufnehmen, das heist, als Makrophagen erscheinen können ist bekannt. . . . Es gibt kaum eine fixe Zelle der tierschen Organismus welche nicht imstande wäre unter Umstanden andere Zellen, Fremdkörper, Parasiten, in sich aufzunehmen und zu verdauen. Sind sie deswegen funktionell gleichwertig? Nicht in geringsten. Es handelt sich hier nur um eine allen Zellen zukommende Teilfunktion, die der

6. Seeman, G.: Ueber den feineren Bau der Lungenalveole, Beitr. z. path. Anat. u. z. allg. Path. **81**:508, 1928-1929.

7. Gardner, L. U., and Smith, D. T.: The Origin of Alveolar Phagocytes Studied in Paraffin Sections of Tissue Stained Supravitally with Neutral Red, Am. J. Path. **3**:445, 1927.

8. Aschoff, L.: Das reticulo-endotheliale System, in Schittenhelm, A.: Handbuch der Krankheiten des Blutes und der blutbildendes Organe, Berlin, Julius Springer, 1925, vol. 2, p. 473.

Verdauung. Also muss man nach anderen Merkmalen suchen. Die Phagocytose ist nur eine bei den uns hier beschäftigenden Zellen (reticulo-endothelial) ganz *besonders stark* ausgesprägte Eigenschaft. Die Intensität, die Häufigkeit der Phagocytose ist hier das entscheidende.

(. . . It is known that occasionally every possible cell will "swallow" coarse foreign elements; i.e., it will act as a macrophage. . . . There is hardly a fixed cell in the animal organism that is not in a position under certain circumstances to swallow and to digest other cells, foreign bodies and parasites. Are they, thereby, functionally identical? Not to the slightest degree. There is concerned here one of the functions proper to every cell, that is, of digestion. One must therefore also look for other characteristics. In the cells with which we are concerned (the reticulo-endothelial) phagocytosis is only one property which is *particularly marked*. The intensity and the amount of phagocytosis are here the deciding factors.)

This conception of phagocytosis, expressed for the first time by Metchnikoff, is at the present time the one accepted by all observers (see also Lubarsch [9]). It is true that the hepatic cell, the renal cell and other fixed cells "engulf" erythrocytes and other foreign elements. However, when stimulated by these substances, these cells do not undergo morphologic changes, and do not proliferate; they do not separate from their customary seat to continue in "the space" their phagocytic activities; they do not take part in the formation of the tubercle (epithelioid cells) in tuberculosis, and do not form giant cells. In brief, their phagocytic properties are only casual and passive, whereas that of the "alveolar epithelium" closely approaches that of the Kupffer cells and that of the cells lining the sinuses of the spleen and the bone marrow. They also apparently take part in the extrahepatic formation of bile.

It is interesting that Seeman, too, although regarding the alveolar cells as epithelial, nevertheless accepted their rôle as essentially defensive. Thus, he wrote: [6]

Es liegt daher der Gedanke nahe, den Ausdruck "respiratorisches Epithel" überhaupt fallen zu lassen und die A-E nur als besonders differenzierte Abwehrelemente zur Beseitigung exogener und endogener Schädigungsfaktoren zu charakterisieren.

(It would be more appropriate to abandon altogether the expression "respiratory epithelium" and to characterize the alveolar epithelium (A.E.) only as elements of defense especially differentiated for the purpose of eliminating exogenous and endogenous noxious agents.)

The interest of this new conception of the pulmonary structure is evident in connection with the respiratory function of the lungs spoken of in the early part of this paper. It also plausibly explains the impossibility of experimentally inducing a generalized or a pulmonary disease by pathogenic micro-organisms introduced into the normal lung by way

9. Lubarsch, O.: Ueber Phagocytose und Phagocyten, Klin. Wchnschr. **4**: 1248, 1925.

of the trachea. No one has been able to produce pneumonia in this way in a normal animal. Only by altering the sensitiveness of the animal has it been possible to cause in the laboratory animal a specific local disease or to overpower the pulmonary barrier, producing septicemia. Thus, when Besredka [10] injected into the lung of the rabbit by way of the trachea "one half a culture on agar" of the paratyphoid bacillus, it was well tolerated by the animal. But when the bacterial infection was preceded by the injection into the rabbit's lung of 0.5 cc. of a 5 per cent solution of bile, "one hundredth of the paratyphoid culture" killed the animal. Bile in the insignificant amount and the weak solution that was used twenty-four hours prior to the bacterial injection causes no changes in the lungs, as revealed under the microscope. The bile in all probability merely alters the normal sensitiveness of the pulmonary "defensive apparatus." Parker and Pappenheimer,[11] too, by infecting guinea-pigs by way of trachea with the pneumococcus, found pulmonary lesions that were mild and transitory. But by "altering the reaction of the guinea-pig," they were able to produce a pneumonic process in this animal. Likewise, Stillman,[12] in inhalation experiments, obtained positive results in the mouse only after the rodent had been previously intoxicated with alcohol.

It is most remarkable that the exquisitely thin and "naked" alveolar wall, which is highly permeable to fluids, is, as a rule, impassable to finely emulsified bacteria, which are, moreover, destroyed in the air spaces. Apparently analogous to the liver and the spleen, the lungs also play a rôle in the defense of the organism, as was indeed demonstrated in the experiments herein reported. As elsewhere in the body, the defensive mechanism of the lungs lies in the pulmonary mesenchyme, of which the cells "lining" the alveoli are an essential part.

SUMMARY

The intratracheal introduction of anthrax bacilli causes no disease in rabbits, provided the extrapulmonary tissues are spared contamination.

The micro-organisms so inoculated are retained by the lungs and are destroyed within a few hours after the infection.

The destruction of the highly pathogenic bacilli is performed by macrophages by way of phagocytosis.

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10. Besredka, A.: Infection et vaccination par voie trachéale, Ann. de l'Inst. Pasteur **34**:361, 1920.

11. Parker, Julia; and Pappenheimer, A. M.: Experimental Pneumonia in Guinea-Pigs, J. Exper. Med. **48**:695, 1928.

12. Stillman, E. G.: Persistence of Inspired Bacteria in the Lungs of Alcoholized Mice, J. Exper. Med. **40**:353, 1924.

The cells found in groups alongside the wall of the air sacs (so-called "alveolar epithelium") play the outstanding rôle in the phagocytosis of the anthrax bacilli.

The experiments have likewise shown that the pulmonary reaction to this "virtual" infection is akin to the "model infections" with vital dyes and oils reported in earlier studies.[1]

This work was made possible through the assistance of Professor Harvey Cushing. The experiments were conducted in the laboratory of Professor Hans Zinsser.

A COMPARISON OF AUTOTRANSPLANTATION, HOMOIOTRANSPLANTATION AND HETEROTRANSPLANTATION OF BLOOD CLOTS*

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In a preceding paper, I analyzed the reactions of the guinea-pig host against autotransplantation and homoiotransplantation of blood clots.[1] I observed that the characteristic differences that are found between the reactions of the host against autotransplanted and homoiotransplanted tissues, if living material is used for the transplantations, are lacking or almost lacking in the case of the corresponding transplants of blood clots; and I concluded, therefore, that living, metabolizing tissue is necessary if one is to obtain typical homoioreactions. In a few preliminary experiments, on the other hand, I found some indications that typical heteroreactions take place also after transplantation of blood coagula, provided that the latter are transplanted into animals of a different species, and I suggested, therefore, that heterotoxins may be given off even by nonmetabolizing, dead tissues. In the present investigations, I wished to test the correctness of the conclusions at which I arrived previously. In the first place, I repeated the homoiotransplantations of blood clots in the guinea-pig and then compared with these various kinds of heterotransplantation of blood coagula in the guinea-pig, as well as in the rat.

AUTOTRANSPLANTATION AND HOMOIOTRANSPLANTATION OF BLOOD CLOTS IN THE GUINEA-PIG

In general, in case of homoiotransplantation of blood clots, the reaction on the part of the surrounding host tissue toward the clot is relatively slight and simple. The host reacts essentially with the mobilization of fibroblasts, which soon surround the clot in a thin layer, and, toward the periphery of the layer, form fibrillar connective tissue, in this way producing a capsule. At the inner aspect of the latter, the fibroblasts remain active and penetrate in various directions into the clot, either turning toward and into it at right angles or forming a network of cells in the clot. In this way, they may penetrate deeply into it.

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1. Loeb, Leo: J. M. Research **37**:353, 1918; Biol. Bull. **40**:143, 1921.

The unfavorable conditions of nourishment and of oxygen supply that obtain within the clot cause many of these cells to perish here. Their protoplasm becomes admixed with the coagulum, and thus a mixture of clot and fibroplasm replaces the pure blood clot. It is this mixture that is gradually organized by newly ingrowing connective tissue cells. The red-staining clot material, to which, as stated, in places fibroplasm is admixed, may reach directly to the connective tissue capsule, to which it is adherent. During the process of organization, changes take place in the coagulum under the influence of the invading host cells, which are arranged here often in the form of parallel and concentric rows. In the course of this provisional organization, the clot may thus be transformed into a homogeneous mass, which then sometimes disintegrates into granular material from which the hemoglobin is washed out. As far as I can make out, the latter changes take place, at least in part, within the invading host cells, which have acted as phagocytes toward this material, and subsequently, when these cells dissolve, a hyaline material remains. At a still later phase of organization, when the invading fibroblasts become more numerous, the material between the cells becomes in part dissolved, and thus vacuolar structures develop between the fibroblasts; fibrils are produced and connective tissue is formed. However, in this organized material, replacing parts of the former clot, some remnants of the coagulum or rather of the coagulum-fibroplasm mixture may still be found in the form of thick fibers, staining red with eosin. Such red, often wavy fibers sometimes envelop a great part of the periphery of the clot, demarcating it from the surrounding connective tissue capsule. Presumably, therefore, these red fibers represent clot material transformed into fibers under the influence of the fibroblasts. In addition, there are other coarse, red-staining fibers in the connective tissue capsule which owe their origin to changes that take place in the muscle tissue on which the transplanted clot has been placed. Here degenerations occur, and the growing and mobile fibroblastic cells may carry necrotic and sometimes also regenerating muscle fibers, with their characteristic chains of nuclei, away from the muscle into the fibroblastic-fibrillar connective tissue, and toward the margin of, or sometimes even into, the clot.

In the early stages of the invasion of the clot by fibroblasts, accompanied perhaps by monocytes, part of the coagulum may take on a bluish stain with hematoxylin, probably owing to the disintegration of nuclear material of the invading cells. Later, from about the seventh day on, central parts of the clot sometimes become converted into hard clumps of a hyaline reddish or greenish material, around which cells of the host tissue form foreign body giant and epithelioid cells. Nearby some fibro-

blasts enlarge, and a fibrillar capsule develops around and between some of these clumps, and together with blood pigment and a few lymphocytes, which are found in the surrounding tissue they may at a relatively late date, from about fifteen to eighteen days after transplantation, represent the last remnants of the clot; occasionally, however, there may still be seen at that time some remaining parts of typical coagulum in process of organization. Within the giant cells can be observed particles of the hyaline hard material or of blood pigment which they have taken up; also within the epithelioid cells and large fibroblasts, such granules may be found. Blood vessels develop in the surrounding tissue and grow toward the remnants of the clot or toward these hyaline clumps. At earlier stages of the organization, branching blood vessels, likewise, may grow into the clot. Rupture of these blood capillaries in certain places may occasionally give rise to hemorrhages in the periphery of the clot, and it is possible that the looser blood coagulum, which is found here and there surrounding the denser red-staining central parts of the coagulum, may owe its origin to such hemorrhages.

Lymphocytes, on the whole, are insignificant in this process. Small collections of these cells may now and then be found around vessels in the connective tissue capsule, or occasionally they accompany the fibroblasts during the process of organization of the coagulum. On the whole, they are an inconstant constituent of the organizing host connective tissue. Likewise phagocytosis, although it may occur after homoiotransplantation of blood clot, is, on the whole, not a prominent feature, and I have not observed phagocytes producing a tissue-like formation here, as they do in the case of heterotransplantation. Also, collections of polymorphonuclear leukocytes, while they are seen occasionally in or around the clot, are rare, and their presence is probably a sign of an accidental local infection of the blood coagulum. Small accumulations of leukocytes, whenever they occur, do not, as a rule, alter the reaction of the host tissue to the transplanted clot, except that near the area of infection the number of lymphocytes may possibly be somewhat greater than elsewhere. Such are the main features of the reactions of the guinea-pig toward homoiotransplanted blood clots. On the whole, these reactions are indications of a simple organization of the clot mainly by fibroblasts, and the development of a relatively thin capsule of fibrillar connective tissue around the coagulum.

HETEROTRANSPLANTATION OF BLOOD CLOTS

I shall now compare with the fate of blood clots after the homoiotransplantation of blood clot that after heterotransplantation. For this purpose, I used clots obtained from the blood of chicken, rabbit and

guinea-pig, and transplanted the coagula into guinea-pigs and rats. The blood was obtained in each case, under aseptic precautions, either from a vein or from the heart of the animals, by means of a syringe, and poured into a petri dish, where it was allowed to clot. It was then kept for from one to two days on ice, after which period pieces were cut out from the coagulum and transplanted into the subcutaneous tissue of guinea-pigs and rats, likewise under aseptic precautions. At various periods of time, what remained of the blood clot, together with the surrounding tissue, was removed for microscopic examination; it was embedded in paraffin and sectioned. The technic used in these experiments was therefore in all essential respects the same as that used previously in the case of homoiotransplantation of blood clots in the guinea-pig.

Observations on Transplantation of Chicken Blood Clot into Guinea-Pig and Rat.—In this series, thirty-four transplanted pieces were recovered and examined. I shall limit myself to a description of the observations at certain selected periods following transplantation.

After Three Days: After three days, a fibrous capsule, which is thin in the rat and, in places, thicker in the guinea-pig, surrounds the clot. In both guinea-pig and rat, large mononuclear cells appear around the dense central nucleated coagulum; they act as phagocytes and take up the nucleated erythrocytes. They also penetrate into the coagulum. In the guinea-pig there are noticeable peripheral areas, in which hemolysis has taken place and only fibers remain; also in the rat there may be in the periphery a network of fibrin, and elsewhere the hemoglobin of peripheral erythrocytes has in part been dissolved, so that only nuclei are left. However, in other places well preserved erythrocytes with hemoglobin are still seen; and, while such cells may also be taken up by phagocytes, it is especially the nucleated hemolyzed corpuscles which are being phagocytosed. Not only the phagocytic cells, but also some fibroblasts and polymorphonuclear leukocytes penetrate into the clot, and around the vessels outside the connective tissue capsule there may be collections of lymphocytes and some polymorphonuclear leukocytes. Especially in the guinea-pig, one finds the latter kind of cells even within the connective tissue capsule.

After Seven and Eight Days: In the period between seven and eight days following transplantation of chicken blood clots into the rat and guinea-pig, one finds, on the whole, similar conditions in both species. One can distinguish four zones in the transplants and in the surrounding host tissue. In the center is a dense nucleated clot. It is surrounded, at least in places, by coagulum showing an early stage of hemolysis; the nuclei are here dissolved. Around this area, one finds a zone in which more marked processes of solution have taken place; there are fibrin

fibers or remnants of large phagocytes that had taken up erythrocytes and thus contributed to the disintegration and solution of the clot. Fibroblasts are moving into this zone, especially along the fibers. There may be here also some polymorphonuclear leukocytes and lymphocytes or macrophages. Surrounding this zone is the connective tissue capsule formed by the host. It is more cellular and richer in fibroblasts and capillaries in the inner part, while it is more fibrillar in the outer layer; between the connective tissue fibers of this capsule, there may be seen some fibrin bands as remnants of the clot, which otherwise has been organized. In some places, collections of phagocytes containing red corpuscles are found within the capsule. It may then be assumed that a considerable part of the original blood clot has been replaced by connective tissue.

The observations on these specimens differ from those in autotransplanted and homoiotransplanted clots, in that in the heterotranplants there is much more infiltration of the connective tissue with lymphocytes, either single ones or groups of them; also polymorphonuclear leukocytes may be here in varying numbers. In places, the connective tissue surrounding the transplant has the appearance of a small cell granulation tissue growing into the clot, and where the solid clot reaches directly to the connective tissue capsule, such tissue may penetrate into it. In other places, fibroblasts enter and spread into the coagulum, contributing to its organization; but especially characteristic are collections of mononuclear phagocytes, which surround the dense clot and even invade it. These cells take up particles of coagulum and thus help to dissolve and destroy it. In the periphery, such phagocytes may be so numerous and may be arranged in such a regular fashion that a tissue-like formation results; it is, perhaps, through secondary disintegration of these cells that, in some cases, the peripheral cavities form, to which I referred.

In other cases, the hyperemic zone and the accumulations of lymphocytes may be less conspicuous or lacking altogether, and one sees merely phagocytes surrounded by a layer of fibroblastic fibrillar connective tissue concentrically arranged around the remnants of the clot, into which numerous fibroblasts may grow in a radial direction. Occasionally seen in the capsule are some peripheral hemorrhages, apparently due to rupture of capillaries of the host. In some cases, cavities are found in the central clot, caused by the activity of large numbers of polymorphonuclear leukocytes. It is possible that, in such cases there is localized bacterial infection in the coagulum; in some peripheral areas it is not always certain what part is played in the processes of solution by the hemolysins, developing or performed in the host, by phagocytes or by polymorphonuclear leukocytes; the latter possibly have been attracted by some bacteria contaminating the transplanted blood clot. Whatever

the mechanism responsible for them, these differences between the homoiotransplanted and heterotransplanted clot, are present notwithstanding the fact that the same technic has been used in transplanting both types of clot, and one is therefore justified in attributing the essential differences, not to accidental bacterial contamination, but to the difference in the reaction of the host to the different types of blood clots.

After Ten and Eleven Days: After ten and eleven days, one finds in the rat conditions similar to those seen in earlier specimens. There is a central clot surrounded by phagocytic cells, which are filled with nuclei of erythrocytes. The clot may reach to the peripheral connective tissue capsule, or it may be surrounded by a zone in which the coagulum has been partly or entirely dissolved and in which there is now seen a net of fibrin fibers, with many phagocytic cells, fibroblasts, some polymorphonuclear leukocytes and lymphocytes. In other places, one finds merely coagulated plasma without cells. In the peripheral capsule, the fibroblasts are usually arranged concentrically, while the capillaries run vertically to the clot; also cells containing blood pigment may be found in this capsule, which is thick and contains masses of lymphocytes and some polymorphonuclear leukocytes. The lymphocytes seem to be especially numerous adjacent to areas in which the processes of solution have taken place. As after seven and eight days, one may find, at this period, mitotic proliferation in the fibroblasts surrounding the remaining parts of the coagulum. The organization of the clot has made further progress; the blood vessels are penetrating into it and the lightstaining, dissolved, as well as the solid, zone is being invaded and replaced by fibroblasts. The phagocytes and in places also the polymorphonuclear leukocytes are helping in this work, being actively engaged in the destruction of the coagulum.

In the guinea-pig, the phagocytes are prominent at this period; they may surround, in tissue-like arrangement, the clot and also fill cavities, the result of solution in the coagulum; fibers of fibrin may be visible in such areas of solution. With the fibroblasts, in certain places, lymphocytes and polymorphonuclear leukocytes enter the coagulum. These cells also may be taken up and digested by phagocytes, although the latter usually are filled with nuclei of erythrocytes. The connective tissue capsule as a rule is usually very cellular, especially in the area adjoining the coagulum. The peripheral dissolved areas seem to have been organized, at least in part. At the same time, the development of fibrillar connective tissue proceeds in the capsule and also in the adjoining muscle tissue; in the latter, leukocytes and lymphocytes may collect and produce injury.

After from Twelve to Fourteen Days: After from twelve to fourteen days, the phagocytic cells are still prominent around as well as inside the

guinea-pig clot and, in places, they may form xanthoma-like tissues. The phagocytosed red corpuscles gradually become dissolved and thus only vacuoles remain in the cell bodies of the phagocytic cells. In certain specimens, polymorphonuclear leukocytes are pronounced and contribute to the processes of solution in the clot. There is always reason for suspecting the presence of bacteria wherever these leukocytes are numerous, especially when they occur in fissures separating parts of the clot. In a few cases, I have actually seen some bacterial colonies in such places; but these were exceptional.

In general, in the guinea-pig as compared with the rat, solution is more prominent, and the number of polymorphonuclear leukocytes in the clot is greater, as is also usually the number of lymphocytes which collect in the surrounding connective tissue capsule. One has to consider in this connection the possibility that, in the guinea-pig, bacterial contamination may have been more frequent than in the rat. The areas of solution seem to decrease in size in the later periods; they have, by this time, probably been organized to a greater or lesser extent.

Observations on Transplantation of Rabbit Blood Clot into Guinea-Pig and Rat.—In this series, altogether forty-three transplants were recovered and examined microscopically, at periods ranging between four and sixteen days following transplantation.

After Four and Five Days: After four and five days mainly connective tissue, with numerous fibroblasts, and a more outer fibrillar zone surround the clot, while fibroblasts and, perhaps, other mononuclear cells invade it; at first, they perish here and subsequently cause a definite organization of the clot. Blood vessels are prominent in certain cases. Polymorphonuclear leukocytes, lymphocytes and larger mononuclear cells other than fibroblasts are variable in number; they may be either numerous or, on the other hand, almost lacking. In some specimens, processes of solution have taken place in the peripheral parts of the coagulum and a network of fibrin fibers alone remains, with polymorphonuclear leukocytes, lymphocytes and fibroblasts invading this area. In such cases one may find, also, in the surrounding connective tissue capsule, a larger number of lymphocytes and some polymorphonuclear leukocytes. It is possible that when larger numbers of leukocytes are present, bacterial contamination has taken place, although clumps of bacteria could not be seen in my specimens. In the majority of pieces, phagocytes are absent or at least are not prominent at this period; but in some cases they can be seen in larger numbers in the rat, either around a central part of the clot or in the more peripheral areas, and they take up red corpuscles. A part of the coagulum has already been replaced by connective tissue at this time. Again one notices two phases in the organization, namely, the phase of provisional organization, in which the

invading cells are destroyed, and a mixture of fibroplasm and coagulum, which paves the way for the second phase of permanent organization.

After Seven, Eight and Nine Days: After seven, eight and nine days, changes observed are not unlike those found after transplantation of chicken clot. Certain features characteristic of heterotransplantation are added to reactions that are similar to those observed after homoiotransplantation. As in the case of homoiotransplantation, one finds a connective tissue capsule surrounding the coagulum. The inner layer of the capsule is richer in fibroblasts which turn toward the clot, while the outer layer is more fibrillar, the fibrillae being, on the whole, arranged concentrically, in contrast with the capillaries, which often run vertically toward the coagulum. Between the fibrils of connective tissue, one may find remnants of the coagulum, in the form either of fibrin fibers, staining red with eosin, or of irregular pieces of clot, which are surrounded by connective tissue; occasionally, the clot remnant has changed into a hyaline material lying between the fibrils of connective tissue. More and more, these remnants of the coagulum are invaded by connective tissue and are thus organized. In other places, one may find blood pigment cells lying in the connective tissue capsule and sometimes extending into the surrounding fat tissue.

One may conclude that the peripheral part of the coagulum has been organized and that it has been partly replaced by the connective tissue capsule. In addition to these fibrin fibers, one may again find remnants of necrotic muscle tissue or sometimes even regenerating muscle fibers carried into the connective tissue capsule by the fibroblasts developing in the surrounding muscle. The fibroblasts are actively proliferating by mitosis. The capsule differs from that found after homoiotransplantation in that it is often thicker, more infiltrated with small cells, especially lymphocytes, and with some polymorphonuclear leukocytes. In some cases, the capsule resembles granulation tissue. From this extreme, one notices all transitions to structures that one sees around homoiotransplants of blood clot. There occur, therefore, variations in different places within the same specimen, as well as in specimens obtained from different animals. The fibroblasts enter the coagulum and may split off parts of it and gradually organize it; lymphocytes and also some polymorphonuclear leukocytes accompany the fibroblasts in certain places. Again there may be found processes of solution in the periphery of the coagulum; in some places, erythrocytes may swell; later solution occurs, leading to the formation of cavities which are traversed by fibrin bands. Some lymphocytes, polymorphonuclear leukocytes and also fibroblasts, the latter often moving along the fibrin fibers, are seen in these cavities. In addition, there are frequently noticed polygonal, finely or more coarsely vacuolated cells with a sharply demarcated cell membrane, evidently phagocytic elements, in appearance not unlike xanthoma cells.

Similar cells occasionally may be seen also within the coagulum. Such phagocytes sometimes contain remnants of cellular material which they have taken up. The presence of these phagocytic cells, the greater number of lymphocytes and also of polymorphonuclear cells and, above all, the solution cavities found in the periphery of the clot, differentiate these heterotransplanted from homoiotransplanted coagula. In some places, the polymorphonuclear cells may be present in larger numbers in the clot and then perish. Also other cellular elements that have entered the clot are destroyed in the dense coagulum and, by means of this provisional organization, help to prepare the way for the later definite organization. Again in these experiments, it is difficult to determine, how far bacterial contamination may be responsible for the greater number of polymorphonuclear leukocytes which one generally finds in such heterogenic coagula. Only in exceptional cases were bacteria actually seen; yet it is probable that also in other cases dense collections of leukocytes are caused by the presence of micro-organisms. In some cases, these cells may possibly also be partly responsible for the formation of the peripheral cavities; but in other areas, it seems that phagocytes help to produce them. The essential factor is, however, in all probability, the hemolytic effect of the foreign serum. As stated previously, such cavities are not usually seen after autotransplantation and homoiotransplantation of coagulum, although in the latter type of transplantation in my experiments the same technic was used as in the case of heterotransplantation. Except for the fact that, after nine days, the greatest part of the coagulum may have been already organized in the rat, one finds no essential difference between the reactions toward the clot in the latter animal and in the guinea-pig.

After from Ten to Sixteen Days: After from ten to sixteen days, the changes are essentially the same as in the preceding period, except that the organization of the coagulum has progressed still further. Fibroblasts move into the coagulum and follow especially the direction of the fibrin fibers. Again the most advanced cells frequently perish; during this process, the nuclei may still remain visible when the cytoplasm has already admixed to the coagulum. With the fibroblasts, lymphocytes often invade the coagulum; the latter are especially numerous around the blood vessels in the frequently thick and densely infiltrated capsule which usually surrounds the coagulum in a concentric direction. The fibroblasts here may show mitoses. As in the preceding period, one may find, between the connective tissue structures of the capsule, remnants of the clot in the form of red-staining fibrin fibers or of hyaline material which later becomes transformed into fibrillar connective tissue through the action of fibroblasts. Prominent at this time are the large mononuclear phagocytic cells, which also may penetrate

into the coagulum and take up red corpuscles or particles of coagulum and occasionally also some leukocytes. After this material has been digested, finally or coarsely vacuolar large cells, forming a xanthoma-like tissue, may remain around the coagulum, which thus, in the course of time, becomes very small. These cells in some cases replace a considerable portion of the coagulum, and they may extend even into the surrounding connective tissue. Only occasionally can giant cells be seen around remnants of the coagulum, which have become hard. Blood pigment cells are found in the capsule, and they wander also into the surrounding fat tissue. Furthermore, some cavities, through which strands of fibers run, are seen between the remaining parts of the coagulum and the connective tissue capsule. The number of polymorphonuclear leukocytes varies in different cases; they may be rare or numerous; and it is possible that some cavities owe their origin to these leukocytes. In other cases, the presence of the xanthoma-like tissue near such cavities suggests that phagocytic cells may possibly have had something to do with the formation of the cavities.

Observations on Transplantation of Guinea-Pig Blood Clot into Rat.—In this series, pieces were examined within a period ranging from seven to twelve days. In principle, one finds here the same conditions as in the case of the other heterotransplantations of blood clots. I shall note merely the principal observations.

After Eight Days: After eight days, one finds a connective tissue capsule around the greater part of the remaining coagulum; its thickness varies in different places. On the whole, the tissue is very cellular, and its fibrillar character is therefore less prominent at this period. Many lymphocytes are seen, especially near the clot, and many large mononuclear cells are around the latter. There are visible various intermediary stages in the transformation of the blood clot into connective tissue, and between the connective tissue cells surrounding the clot, I find red-staining fibers that represent remnants of coagulum or mixtures of coagulum and the protoplasm of degenerated fibroblasts. Such red-staining fibers may envelop the coagulum and somewhat further toward the periphery a net of fibers appears, between which rounded off fibroblasts or monocytes are enclosed. There are also areas that represent a mixture of coagulum and cell protoplasm; one deals here with intermediate stages in the organization process. In the periphery of the capsule, where lymphocytic infiltration is noticeable, blood pigment cells appear; during the organization process, they carry particles of hemoglobin derivatives away into the surrounding tissue. Near the clot, there are again pieces of yellow-stained, solid particles of coagulum with many giant cells, in some of which the nuclei have become pyknotic. While

the connective tissue cells are arranged concentrically around the clot, the blood vessels run as usual in a radial direction toward the coagula.

After Eleven Days: After eleven days, one finds again, in the fibrous tissue capsule, some remnants of clot in the form of hyaline material, as well as of hemoglobin-containing particles of coagulum. Likewise there are, in places, in the connective tissue capsule, large masses of lymphocytes, as well as some polymorphonuclear leukocytes and blood pigment cells. Phagocytes, epithelioid in appearance, replace parts of the clot; and again there are red-staining fibers, presumably representing a mixture of fibroplasm and coagulum, around the coagulum, and the majority of the cells between the fibers are phagocytes, containing pigment in various stages of disintegration. The cells that have penetrated farthest into the coagulum are already destroyed. The provisional organization is therefore still proceeding; subsequently, the organized material is transformed into connective tissue. Also at this period, some red and yellow pieces of hard material, around which giant cells and connective tissue fibers are seen, develop from coagulated material. In other specimens, such pieces of pigmented hard blood clot, together with foreign body giant cells, epithelioid cells and lymphocytes, are the principal remnants of the blood clot. In some places there can be seen a pronounced lymphocytic infiltration, while in other places vacuolated cells surround the coagulum. In the interior of the phagocytic cells, pieces of coagulum, which they have taken up, become granular, and this change represents a step in the solution of the coagulated material. The whole is enclosed in a fibrillar or fibrous connective tissue capsule.

COMMENT

My aim in this paper was to compare with the transplantation of living tissues, which were studied in a preceding series of papers, the transplantation of cells which have genetically the same constitution as other cells of the same organism, but which soon after transplantation cease to maintain their specific metabolism and gradually undergo disintegration and solution. The problem was whether such material would call forth the same autoreactions, homoioreactions and heteroreactions as were found in the case of ordinary metabolizing tissues. Do the individuality differentials function in such cells as they do in the case of normal tissues?

I therefore transplanted into the subcutaneous tissue of the guinea-pig blood clots from the same guinea-pig (autogenous blood clots), as well as from other guinea-pigs (homoiogenous blood clots). Furthermore, I carried out various kinds of heterotransplantations. In the case of autotransplantation and homoiotransplantation, I found relatively simple reactions on the part of the host tissue. The fibroblasts of the

host capillaries invade the coagulum; they form first a provisional organization leading to a mixture of coagulum and fibroplasm, which is then definitely organized by fibroblasts growing into this material somewhat later. This provisional organization leads to the formation of various structures, as, for instance, fibers staining red with eosin, representing mixtures of coagulum and of the protoplasm of fibroblasts. Similar structures are also found after transplantation of heterogenous coagula; and both after homoiotransplantation and heterotransplantion there occur, in the fibrillar capsule surrounding the clot, remnants of the blood coagulum in the form of red-staining strands of pale hyaline material. Capillaries participate in the process of organization. There are occasionally some lymphocytes visible in the tissue sorrounding the clot and accompanying the fibroblasts in their invasion of the clot, but on the whole, they are inconspicuous. While one cannot exclude the possibility that a slight difference exists between autotransplantation and homoiotransplantation, it certainly is not comparable to such differences as one finds after transplantation of living tissues. Phagocytosis occurs during the organization of the homoiogenous blood clot, but it is not a conspicuous process; however, phagocytes help occasionally in transforming the coagulum; within these cells, the particles of clot are first split into granules, which then, after the disintegration of the cells, coalesce to form a hyaline material. Polymorphonuclear leukocytes do not play a significant rôle, and whenever they are prominent one is justified in assuming a contamination of the coagulum with bacteria. One may, therefore, conclude that the typical homoiotoxins are not in any considerable quantity given off by the nonnucleated erythrocytes of a blood clot. Evidently living and metabolizing cells are necessary for this purpose.

Conditions are different after transplantation of heterogenous blood clots, the reaction of the surrounding host tissue being in this case much more pronounced. Admixed to the connective tissue, surrounding and invading the clot, there are generally considerable numbers of lymphocytes, and the capsule around the coagulum is usually thicker than after homoiotransplantation or autotransplantation; however, the number of lymphocytes, as well as the thickness of the connective tissue capsule, vary in different experiments, as well as at different points around the same coagulum. Furthermore, there are areas with partial solution of the clot, in which various stages in the process of solution can be recognized. A further distinction between the reaction of host tissue against homogenous and heterogenous clots is the greater prominence of phagocytic cells in the latter type. Phagocytes take up particles of heterogenous clot containing erythrocytes and gradually dissolve them within their cell bodies. Such phagocytic cells are frequently seen in great

numbers and occasionally form a tissue, in appearance not unlike xanthoma. Around or invading the coagulum, there are often present polymorphonuclear leukocytes. These cells are much more prominent after heterotransplantation than after homoiotransplantation. While it is possible and even probable that in some cases contamination with bacteria is the cause of the increased number of these leukocytes, I do not believe that this factor is solely responsible for it, because my technic was the same after homoiotransplantation and heterotransplantation. In this connection, I must recall the fact that, also after heterotransplantations of ordinary tissues, polymorphonuclear leukocytes are more prominent than after homoiotransplantation. As to the processes of solution which take place in the heterogenous coagula, they are probably largely due to the action of the heterogenous serum of the host; as an indication that such a process occurs, one may consider the swelling of erythrocytes, which I was able to observe in one specimen, and which I consider as a first step in the solution of the coagulum. However, it is probable that, in other cases, phagocytic cells or polymorphonuclear leukocytes contribute to the solution or cause it altogether.

One sees then that heterogenous blood coagula call forth much more active reactions on the part of the host tissue than do autogenous and homoiogenous coagula. Evidently heterotoxins are found also in dead cells, and may gradually be extracted from the latter, and thus cause reactions on the part of the host. These heterotoxins, being more active than homoiotoxins, exert an influence not only on the sensitive lymphocytes, which react to slight chemical alterations in the environment, but also on the polymorphonuclear leukocytes, which respond to stronger poisons.

My results confirm thus my earlier conclusions as to the difference in the character of homoiotoxins and heterotoxins, and they are also in agreement with the experiments of Siebert,[2] who found, in this laboratory, that typical heteroreactions can be obtained from cartilage subjected to moderate degrees of heat, sufficient to cause the death of the heterotransplant, whereas after homoiotransplantation a reaction was obtained only in case the transplant remained alive. Moreover, the interaction which in this case takes place between substances present in the blood serum of the host and the transplanted heterogenous material, leading to processes of solution, accentuates the reactions of the host cells against the transplant.

There are some quantitative differences in the effects caused by various types of heterogenous blood clots, but, in general, the reactions are very similar in character. One may therefore conclude that dying or

2. Siebert, W. J.: Proc. Soc. Exper. Biol. & Med. **26**:238, 1928.

dead heterogenous transplants may still exert a specific effect on the host tissue, whereas the specific homoioreaction is no longer fully developed under these circumstances.

SUMMARY

The simple processes taking place during the organization of autogenous and homoiogenous blood clots are contrasted with the much more complex processes observed during the organization of heterogenous blood clots. The various types of reaction that occur in the latter case, represent reactions to heterotoxins, which remain active even in dead or degenerating tissue, in contrast with homoiotoxins, which are active only in case of continued life and metabolic activity of the transplant.

Laboratory Methods and Technical Notes

A COMPARATIVE STUDY OF CERTAIN METHODS FOR THE ESTIMATION OF HEMOGLOBIN*

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Although numerous methods have been introduced and recommended for the determination of the hemoglobin content of the blood, they still possess certain inherent difficulties or faults that leave much to be desired. The methods more commonly employed are subject to varying degrees of inaccuracy, so that the results obtained by the technic in one laboratory are often not comparable with those obtained in other laboratories by the same or different technics. While other methods are accurate and furnish data that may be duplicated, they require more time, equipment and care than many laboratories can afford.

The satisfactory technic for the estimation of hemoglobin, therefore, should include in its performance a minimum requirement of time, simplicity and facility of operation, and an accuracy such that results obtained can be duplicated. A study has accordingly been made of various methods, and a technic has been adopted which appears to fulfil the conditions stated.

METHODS

In this report, we include only the gasometric technic of Van Slyke and Stadie,[1] the iron method of Wong,[2] the more recent colorimetric method of Newcomer[3] (the use of a colored glass plate and filter) and one modification of the Newcomer method. Estimations of the red blood cells have also been made in order to supply another means of comparison.

The modification that we have made of the Newcomer method consists of (1) the use of 2.5 cc. of diluent (approximately tenth-normal hydrochloric acid) instead of 5 cc. and (2) the use of two colored glass plates which are glued together. The same amount of blood, 20 c.mm., was used. The details of the determination, therefore, are: (1) 20 c.mm. of blood is added to 2.5 cc. of diluent; (2) after this is mixed, it is allowed to stand thirty minutes; (3) the blood mixture is transferred to one cup of a colorimeter, while distilled water is added to the other cup, and the double glass plate is inserted under the latter. The colorimeter used is the Bausch and Lomb microcolorimeter (no. 3265), and light conditions are kept uniform by employing a Palo daylight colorimeter lamp.

In order that the readings obtained by the colorimeter may be readily translated into grams of hemoglobin per hundred cubic centimeters of blood, a table is prepared in which are given the values of hemoglobin representative of the differ-

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* From the Laboratory of the Monmouth Memorial Hospital.

1. Van Slyke, D. D., and Stadie, W. C.: J. Biol. Chem. **49**:1, 1921.

2. Wong, S. Y.: J. Biol. Chem. **55**:421, 1923.

3. Newcomer, H. S.: J. Biol. Chem. **27**:465, 1919.

ent readings. These values are derived from the formula given by Newcomer[3] $3\frac{0.38\ d}{t}$ in which d equals the dilution of the blood (251) and t the reading of the colorimeter in millimeters. A correction for the thirty minute interval during which the diluted blood is allowed to stand before being read has been computed to be 1.5 per cent more than the value obtained directly from this formula.

EXPERIMENTAL RESULTS

The results of previous experience with the original Newcomer color plate method were unsatisfactory, because the color elicited was too pale for matching the hues in more commonly encountered ranges. For this reason, the double plate method, as described, was adopted.

TABLE 1.—*Results of Different Methods of Deriving the Hemoglobin Value of Blood*

Specimen of Blood (Different Persons)	Van Slyke's	Pons-Newcomer	Wong's	Newcomer's	Erythrocyte Count	Percentage of Error
1	14.40	14.2	14.8	....	.....	—1.38
2	12.62	12.7	13.0	....	3,820,000	+0.63
3	12.39	12.7	19.0	....	3,900,000	+2.50
4	12.56	12.9	13.0	....	4,950,000	+2.61
5	11.60	11.9	12.0	....	3,860,000	+2.59
6	16.53	16.4	16.6	....	.....	+0.78
7	12.82	12.9	12.3	13.99	4,630,000	—0.62
8	14.54	14.72	14.5	16.55	4,540,000	+1.30
9	13.70	14.0	14.6	16.5	3,750,000	+2.19
10	13.90	14.3	14.6	17.0	4,060,000	+2.87
11	10.20	10.6	10.7	12.0	3,330,000	+3.90
12	15.90	16.1	16.4	19.0	4,850,000	+1.25
13	14.70	14.9	15.1	17.53	3,900,000	+1.35
14	12.64	12.9	12.8	14.6	4,040,000	+2.05
15	10.32	10.6	10.7	10.7	3,850,000	+2.71
16	13.48	13.6	14.0	14.0	3,620,000	+0.89
17	12.90	13.1	13.0	13.0	3,790,000	+2.39
18	10.64	11.0	11.5	11.5	3,900,000	+2.90
19	13.76	13.8	14.0	14.0	4,820,000	+0.29
20	14.96	15.1	15.4	15.41	4,320,000	+0.93

Mean average error between Van Slyke's oxygen capacity and Newcomer's +1.80 per cent.

Observations have been made on specimens of blood from twenty different persons. Sufficient blood was collected by venipuncture in tubes containing sodium oxalate so that hemoglobin values might be determined at the same time by the four different methods enumerated (table 1). The results reveal that the values obtained by the modified Newcomer method vary from those obtained by the Van Slyke and Stadie method, by a minimum deviation of 0.29 per cent and a maximum of 3.90 per cent. The average variation for the twenty determinations, however, is only 1.80 per cent.

The value obtained by the modified Newcomer method approaches more closely the Van Slyke value in sixteen instances, while the Wong method gives more nearly the accurate figures in four instances. The differences in the results obtained by the Wong method and the modified Newcomer method are not sufficiently great to justify the assumption that the latter method insures more accurate results. The facility of the modified Newcomer method, however, renders it preferable. In none

of the determinations did the newer modification of the Newcomer method give the value closest to that obtained by the Van Slyke method.

The normal standard of hemoglobin as given by different authors (table 2) shows marked variations. The more commonly employed value is Haldane's, which is given as 13.89 Gm. per hundred cubic centimeters of blood. Williamson accepted the much higher value of 16.8 Gm. A study of the data in table 1 discloses that Haldane's figures are indeed too low for a normal standard. We have accepted the Haden standard (15.8 Gm.) as the normal.

TABLE 2.—*Hemoglobin Content of Blood Considered as Normal by Different Investigators Using Different Methods*

Investigator	Men Studied	Average Normal Value
Sahli, quoted by Kern, R. A.: M. Clin. N. Amer. **8**: 129, 1924..	Not stated	17.20
Williamson: Arch. Int. Med. **18**: 505, 1916.....	36	16.80
Haden, R. L.: J. A. M. A. **79**: 1496, 1922.....	20	15.83
Osgood, E. E.: J. Biol. Chem. **57**: 107, 1923.....	137	15.76
Haldane, J.: J. Physiol. **38**: 1133, 1901.....	12	13.89

COMMENT

This report comprises a comparative study of the determination of hemoglobin in the blood with the Van Slyke and Stadie method as the standard. This method was compared with the iron method of Wong, the Newcomer technic in its latest form (i. e., the use of a colored plate and filter) and our own modification of the Newcomer method as described. It has been found that the modification suggested most nearly approximates the values derived by the Van Slyke method. The average deviation from the Van Slyke method in determinations in twenty persons was only 1.80 per cent. In addition, it is performed with ease, and it gives similar results on repeated determinations.

The values reported in this study have been given in grams of hemoglobin per hundred cubic centimeters of blood. This we consider a more accurate and more appropriate manner of expressing the determinations than that more widely employed, i. e., in percentage of hemoglobin. The custom of stating the quantities of the chemical constituents of the blood in grams per hundred cubic centimeters of blood establishes a precedent which should include hemoglobin values also. It has been our custom to report hemoglobin determination in grams rather than "per cent" in a large hospital laboratory and more recently in the present laboratory. In both instances, the changes were readily accepted.

SUMMARY AND CONCLUSIONS

A modification of the Newcomer colorimetric method for the determination of hemoglobin in the blood is described. This modified method gives values varying on an average 1.80 per cent from those derived by the Van Slyke and Stadie method. It is managed with facility; it does not require expensive equipment; is not time consuming, and the standard is permanent.

It is suggested that hemoglobin values be expressed in grams per hundred cubic centimeters of blood.

General Review

SMALLPOX AND VACCINIA

THE PATHOLOGIC HISTOLOGY*

DEDICATED TO DR. W. T. COUNCILMAN IN HONOR OF HIS SEVENTY-SIXTH BIRTHDAY

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But little of present importance in the pathologic histology of smallpox was described before the European epidemics of 1870 and 1872. The most attention has naturally enough been devoted to the lesions of the skin, but a considerable number of authors have described also focal lesions of the various internal organs. Recently, these focal lesions have been strikingly paralleled by visceral lesions produced experimentally in rabbits by the use of especially virulent vaccine viruses, the effects of one of which I have had the opportunity of studying in detail in about 150 animals. This study is being reported eleswhere and will be referred to only briefly in this communication.

Owing to the rather considerable number of references on the subject, it was thought desirable to discuss the various organs affected individually, more especially as that plan was followed in the comprehensive review given in the great work of Councilman, Magrath and Brinckerhoff (1904). I have attempted to make this review equally comprehensive, and must here express my regret that it was necessary to derive many of the earlier references from reviews, as they were not available in their originals.

SKIN

Bärensprung described four stages in the evolution of the pock. First were seen widening of the blood vessels of the skin, elongation of the papillae, thickening of the rete and consequent epithelial elevation to form the papule. Next followed swelling of the rete cells with fluid exudate, formation of a thick wall laterally and, centrally, separation of the cells so that they floated free in the vesicle space between the stratum corneum and the papillae. In pustulation, the lower part of the rete was destroyed by suppuration. The fourth, inconstant

* From the Hygienic Laboratory.

stage, comprised ulceration. According to Auspitz and Basch, the vesicle was formed by a reticulum containing in its meshes fluid and pus cells. Both these and the reticulum were considered as derived from the epithelium. Umbilication was explained as due to changes in the epithelium and to evaporation from the central portion. Klebs saw a reticulum formed in the middle layers of the epidermis through the separation of the epithelial cells by fluid and cellular exudate.

Rindfleisch described serous exudation proceeding up from the papillae, separating the cells and forming vertical or oblique trabeculae in the thus formed vesicle. The swollen cells in the lower layers of the rete next gave rise to pus cells, which filled the vesicle space; later in some cases there was suppuration with destruction of the papillae. Luginbuhl called attention to the presence of multinucleate giant cells.

Zuelzer and also Ponfick reported cutaneous hemorrhages in hemorrhagic smallpox, but gave no histologic details.

Weigert first introduced the concept of primary coagulation necrosis with subsequent leukocyte reaction. He also first studied the histologic relation of bacteria to the pock and first described the inclusion bodies later brought into such prominence by the work of Guarnieri and others following him. Weigert found primarily a diphtheroid necrosis in which the cells of the lowest layer of the epidermis were necrotic, but not broken down. Laterally and above these, fluid collected between the cells and caused the umbilication by the greater swelling in the periphery of the pock than in the coagulated necrotic central basal portion.

Cornil saw cavities arising within the epithelial cells forming a reticulum composed of the cell peripheries. The cell content of these spaces was derived partly from epithelial proliferation and partly from emigration from the corium.

Leloir noted in the papular stage the formation of a clear perinuclear zone in the cells especially of the middle of the rete. This space enlarged, and the contained nucleus fragmented and disappeared. Next there was fusion of these intracellular spaces with invasion by pus cells from the corium. Fibrin was seen in the space of the vesicle as a fine network. For details of Renault's work on the development of the pock I am indebted to the reviews of Burchardt, Unna (1882) and Councilman. He described edema and dilatation of the papillary lymphatics. Prickle cells above the basal layer showed first perinuclear vacuolation, then swelling to large vacuoles and fusion of these to form the vesicle, the trabeculae being made up of condensed cell peripheries and cement substance. Centrally, the rete cells showed granular degeneration, and later, necrosis and liquefaction of the basal cylindric cells; peripherally, there was vacuolation like that in the upper prickle cell

layer. During the conversion of the vesicle into the pustule, there was capillary engorgement in the papillary bodies, with emigration of leukocytes and invasion of the vesicle by these. There was breaking down of the corium under the pustule. Renault described in the prevesicular stage numerous round refractile bodies, uniform in size, which on the warm stage grew into short "branches" composed of a row of similar spherules. These he considered parasitic. They were found in the perinuclear zone of isolated prickle cells, the latter often in the process of reticulating colliquation.

Touton described several rather early pocks. These were not dissimilar from the vaccine pustule described by him (q. v.). Hemorrhage was lacking, the necrotic cell masses described first by Weigert were less numerous, the trabeculae were thinner, the basal prickle cells were often normal or little swollen, and the round cells were more numerous. Near the lateral margin of the mesh work were poorly stained foci with poorly defined nuclear and cellular outlines breaking down to vacuoles filled by granulofibrillar material. This change he designated as cloudy swelling. He also noted a fibrinoid degeneration of some of the epithelial cells.

Guarnieri described his *Cytoryctes variolae* and *vaccinae* with several phases, which he considered as evidence of the protozoal nature of these inclusions. As this subject was recently critically reviewed in the ARCHIVES by Goodpasture, I will not attempt to cover again the extensive literature which has arisen on the nature and significance of these bodies.

Buri, working in Unna's laboratory, described in detail the evolution of the pock and reviewed the literature on the subject. His description of the epithelial changes follows Unna's so closely that it hardly appears necessary to cite it in detail. He saw much infiltration of the corium with pus cells even in very early stages. These leukocytes were especially numerous in the papillae and along the blood vessels and glands. Edema and dilatation of lymph and blood vessels appeared early and became more pronounced in the acme of the process. Necrosis or destruction of the derma or papillae was not seen in Buri's preparations, nor did he find any diphtheroid necrosis of the epithelium. In this connection, it should be noted that Buri's material comprised several pustules from one autopsy and specimens taken for biopsy, at various stages of the disease, apparently largely from discrete cases, but in at least one from a confluent case. MacCallum and Moody in material taken from alastrim for biopsy, and Sweitzer and Ikeda in material taken for biopsy, from their discrete cases also saw a marked and early leukocyte reaction and lack of necrosis in dermis and epidermis.

The description of the pock by the late Professor Unna (1894) is considered classic, and as some of the terms used by him appear to

have been misinterpreted in more recent literature, I will attempt to summarize his account. In the papular stage, "reticulating colliquation" occurs in the upper portion of the prickle cell layer of the generally edematous epithelium. This begins in cytoplasmic vacuoles and is followed by fibrinoid degeneration. Vertical trabeculae of epithelial cells are left. In the lower portion of the prickle cell layer, "ballooning degeneration" occurs. In this process, the epithelial cells separate and round up into rounded masses ("balloons") containing one or two nuclei, rarely more. The vesicle extends above by a breaking down of the edematous cells. Ballooning extends less. The next step is fibrinoid degeneration of the trabeculae and "ballooned" masses. Necrosis does not necessarily ensue. In the corium, dense perivascular infiltration with large vacuolated plasma cells occurs in the papulovesicular stage. On the fifth day the blood vessels of the skin dilate; emigration of leukocytes follows; these invade the vesicle and convert it into a pustule. Suppuration ensues when the horny layer breaks down. Otherwise, the pustule dries, and the epithelium grows in under the pock from all sides, cornifies upward and finally pushes off the crust. Unna did not describe pocks in which destruction of the underlying corium occurred.

Bosc found the lesion of the skin in smallpox essentially like that in vaccinia. Stokes noted the frequent exudation of fibrin into the pock. Councilman, Magrath and Brinckerhoff observed first nuclear swelling with chromatin clumping in the epithelial cells. Cytoplasmic inclusion bodies were often present. Reticular degeneration ensued, in which cell vacuoles formed, then ruptured and fused to form vesicles. The trabeculae were formed by condensed cell peripheries. The lowest cells in the center of the pock underwent "hyaline fibrinoid degeneration" in which they swelled and rounded up singly or in masses and then became hyaline and refractile, reacting as fibrin to the Weigert method. Only in the later stages did polymorphonuclear leukocytes appear in the vesicle. At this time also were noted perivascular infiltrations in the corium. These consisted of polymorphonuclear leukocytes and large basophil cells. The latter, in part, were identified with Unna's plasma cells. Judged by Councilman's excellent illustrations, the large basophil cells to which he so often refers appear to comprise both plasma cells and large lymphoid cells with nucleoli, leptochromatic nuclei and broad basophilic cytoplasm, apparently of the same type as those referred to by Pappenheim as lymphoidocytes. Larger lesions showed complete destruction of the basal epithelium in the center, and necrosis of part of the corium. The healing occurred essentially as described by Unna. Purpuric cases showed hemorrhages in the corium, numerous streptococci in tissues and blood vessels and widespread reticulating degeneration of the epithelium. Many inclusions, both

nuclear and cytoplasmic, were present. Mitoses were frequent in non-reticulated areas.

Ferguson described incompletely septate vesicles. The septums, he believed, arose in part by proliferation of papillary epithelial buds from the malpighian layer. The pustule contents he found to be about half polymorphonuclear leukocytes and half small hyaline cells. In cases in which the pocks were confluent, almost continuous vesicle formation occurred over wide areas. There were swelling and degeneration of the dermal collagen, infiltration by blood corpuscles and mononuclear leukocytes and frequent small intra-epidermic abscesses. Healing was described essentially as by Unna.

Schrumpf, in a dissertation mainly devoted to the description and discussion of Guarnieri bodies and their significance, described briefly the histogenesis of the pock. There was proliferation of the malpighian layer followed by a central breaking down, exudation of fibrin and invasion by cocci. Later, the margins showed varying amounts of vacuolization of the proliferated epithelium; the center, a trabeculated space filled by degenerated epithelial cells, leukocytes, fibrin, cocci and débris.

Heinrichsdorff studied the lesions of the skin in hemorrhagic smallpox, not including purpura variolosa. One type of lesion showed, first, edema in the corium, with foci of small and large round cells, small hemorrhages and emigration of leukocytes. This swelling and infiltration flattened out the rete pegs of the epidermis, producing thereby a papular elevation. In some of these lesions there was also exudation of fluid between the corium and epidermis; in others, small droplets of fluid appeared in the cytoplasm of the epithelial cells, compressing and displacing their nuclei, but not fusing to form vesicles. At the same time there was marked proliferation in all layers of the epidermis. Another type of lesion showed complete coagulation necrosis of the entire epidermis. In this, indistinct spaces appeared in the fused necrotic cell mass, the larger of these being filled with blood and polymorphonuclear leukocytes. Marginally, such lesions showed vacuolar degeneration of the epithelium. In the corium, there were hemorrhages, disruption of tissue and necrosis, capillary swelling, degeneration and thrombosis. Beneath larger pocks, there were capillary lesions and edema in the corium, vacuolation of the basal layers of the epidermis, and next to these, necrotic cells surrounded by epithelial giant cells each with many small nuclei or a single giant nucleus. Above these was a zone of degenerating cells breaking down to form detritus-containing spaces. Elsewhere were seen epithelial syncytia with scattered pyknotic nuclei. Necrosis and vesiculation occurred indiscriminately in all parts of the epithelium beneath the horny layer. The hair follicles also showed necroses and epithelial giant cells. Also the sebaceous

glands showed necroses. These were first surrounded by exudation of fluid and polymorphonuclear leukocytes. Later, either they formed and extruded a crust by downgrowth of epithelium or there occurred round cell infiltration and scarring. This report of the necrosis of sebaceous glands appears to be unique in the literature of smallpox. I have seen involvement of the glands of the skin in the coagulation necrosis of the corium in the local lesions of virulent vaccina in rabbits, as I believe have also Ledingham and Barratt, and Bijl and Prenkel, though they make no specific statement, and focal glandular lesions, as well, among the lesions produced by the Calmette-Guerin reaction.

MacCallum and Moody studied a small number of specimens taken for biopsy from alastrim in Jamaica. In the early stages, there were edema and dense perivascular infiltration of the corium. The infiltrating cells were polymorphonuclear leukocytes and mononuclear cells, including definite plasma cells. At the site of pocks, the epithelium was "relaxed and separated into loose cells." There appeared between the cells spaces which were "generally loaded with leukocytes." There was vacuolation which often appeared to be intranuclear, and there was often necrosis of overlying cells, but central basal coagulation necrosis was not observed. The corium was usually denuded in the center of the pock. Inclusions resembling those described by Guarnieri and others were seen. Healing occurred as in smallpox. The marked cellular inflammatory reaction in these cases is noteworthy and comparable only with that in Michelson's and Ikeda's benign case.

Sörensen and Sörensen, in a case of purpura variolosa with a hemorrhagic exanthem, noted the usual picture of the early pock and streptococcal thrombi. The account of Michelson and Ikeda presents few variations from those of Unna and Councilman. Interepithelial perpendicular rifts were seen when much edema was present. Some reticulation was noted in the deeper parts of the horny layer. Destruction of elastic tissue was noted in the scars in cases in which recovery had taken place, contrary to the statement of Unna that elastic tissue did not degenerate. Their benign case showed much more cellular infiltration of the corium than most of the fatal cases. In purpura variolosa, Ikeda saw cutaneous hemorrhages, some perivascular mononuclear infiltration, cloudy, edematous swelling of the epithelial cells with separation of the basal layer by serous exudate, areas of ballooning and reticular degeneration and early vesicle formation.

The histology of the lesions of the skin in vaccinia has been studied principally in animals, chiefly the calf and the rabbit. But few publications dealing with these lesions in man have appeared.

Kierle described the vaccine crust as a slough of the skin in which were distinguished histologically from above down a layer of epidermal

scales, the blood tinged cells of the rete mucosum, the likewise blood tinged papillae and interpapillary furrows, the hair follicles and elastic tissue and last a wide-meshed, coarse-threaded, branching connective tissue showing excessive cell proliferation on its trabeculae and containing sweat glands and ducts.

Touton described a vaccine pustule ten days after inoculation. Fairly dense small cell infiltration was noted in the cutis, with some hemorrhage in the papillary body and above this an irregular meshwork with coarse trabeculae of mostly nonnucleated, compressed epithelial cells and a finer meshwork corresponding to individual cell walls. In the mesh spaces next the cutis were dense masses, granular toward the center, often with traces of a nucleus. Above these, in the larger spaces, were cells with well stained nuclei, masses similar to those in the basal layer and granular and fibrillar débris; also some wandering cells. Toward the roof were large cells with swollen, pale nuclei, breaking down to form further spaces; laterally, in the upper part, were swollen cells with clear vesicles containing sickle-shaped chromatic areas in the place of nuclei; lower, a "compressed epithelial cord." Marginal proliferation was not noted.

Gaucher observed a fatal case of generalized vaccinia in an infant 1 month of age. There was a generalized pustular eruption. At autopsy, the lungs were intensely congested, the spleen was enlarged and soft, and the liver was flecked with foci of fatty degeneration. No histologic observations were reported. Death occurred on the fifteenth day after vaccination or the sixth day of the general eruption. Calf virus was used.

Buri studied vaccine pustules removed on the fifth, sixth and eighth days from an infant. The vesicle space was already large on the fifth day, the roof thin, the floor made up partly of naked, partly of epithelium-covered, well preserved papillae. Only a few vertical or oblique trabeculae of compressed cells were present. Ballooning degeneration, though seen chiefly in the lower layers, was not confined to this area and was generally much more extensive than in variola. Reticulating degeneration was also seen in all layers, though again principally in the upper ones. Laterally, as in smallpox, there were marked proliferation and edema of the epithelium. Leukocyte infiltration both in the pock cavity and in the cutis was much less extensive than in variola. Coagulation necrosis of epithelial cells was seen only along the line of the inoculation. Multinucleated "balloons" as in variola showed two and three nuclei, but not more. Balloons showing peripheral reticulation of their cytoplasm were seen in the eight day pustule.

Unna (1894) found that ballooning colliquation played a much larger part in vaccinia than in variola. Four to six rows of such rounded, ballooned epithelial cells were seen on the roof. The vesicle

space lay more in the middle of the prickle cell layer. The ballooned masses on the floor of the vesicle were more often multinuclear than in variola. Above and lateral to the areas of ballooning was found the reticulating colliquation seen in smallpox. Some of the marginal "balloons" in the roof sometimes showed the vacuolation of the reticulating type of degeneration in their outer portions. The region of the inoculation wound showed a vertical strand of Weigert's coagulation necrosis, the cells comprising it having lost their nuclei and undergone fibrinous degeneration. The cells of the septums were less flattened and compressed than in variola and appeared to represent remnants of the ducts of the sweat glands. Suppuration was late and relatively slight; the vessels of the derma were widened only to the depth of the papillary body; the swelling of the connective tissue cells was similarly superficial; plasma cells were absent; emigration of leukocytes was slight, even at the height of the process when compared with variola. The peripheral reticulating colliquation was much less than in variola. Healing occurred as described in variola. The comparative lack of necrosis of epithelial cells and the slight reaction in the derma contrast sharply with the much more severe injury of tissue described by Turnbull and McIntosh thirty years later.

Cory vaccinated supernumerary digits of children and amputated these at varying intervals after the vaccination. In this material, he saw in the papular stage an increase in the size and number of the epithelial cells and an increase of intercellular fluid, especially between the round epithelial cells of the rete malpighii. As the lesion developed, this process spread peripherally, while centrally the excess of intercellular fluid and the rupture of some of the large cells produced vacuoles, while other cells were compressed into flattened and spindle forms to make up the trabeculae of the vesicle. These changes progressed successively toward the periphery; centrally, fluid absorption occurred, and the cells became smaller. Fibrinoid degeneration, necrosis, ballooning and leukocyte invasion were not mentioned. An areola appeared around the vesicle about the eighth day, and about the tenth day a new stratum lucidum appeared marginally and extended beneath the vesicle, finally pushing off the scab. Changes in the dermis were not described.

Ewing, comparing the lesions of the skin in vaccinia and variola, concerned himself mainly with the cell inclusions, which he considered, for the most part, degeneration products.

Howard and Perkins described the histology of vaccinia as based on twenty-five specimens taken for biopsy from twelve vaccinated adults. In forty-eight hours, a cup-shaped vesicle traversed by an eosinophilic reticular meshwork had appeared. The horny layer formed the roof; the floor, centrally, was bare corium, with cells laterally in hyaline

fibrinoid degeneration, and other forms of degeneration marginally. The hyaline fibrinoid cells were intensely oxyphil, hyaline and often elongated, their nuclei shrunken and pyknotic. The marginal basal cells were swollen, reticulated or granular, sometimes vacuolated, their nuclei swollen, with the chromatin clumping or shrunken, pyknotic or fragmented. In the lateral wall were seen swelling of cells, loss of prickles, inclusion within epithelial cells of other epithelial cells and of mononuclear leukocytes. Between the basal cells and in hair follicles and sweat glands there was invasion by red cells, small and large mononuclears, polymorphonuclear neutrophils and especially eosinophils. Marked edema of the papillae was noted, also free red cells, mononuclear and polymorphonuclear leukocytes, hyperemia, capillary endothelial proliferation and desquamation. There was marked perivascular infiltration by leukocytes, but no necrosis or abscess formation. On the third day, leukocytes invaded the lower parts of the vesicle; this extended laterally by hyaline fibrinoid and reticulating degeneration; the inflammatory reaction in the corium was more marked. The reticulum became more and more condensed, the invasion of the vesicle by leukocytes progressed, and necrosis of epithelium and leukocytes advanced until, by the fifth day, there was a crust of dense, homogeneous, deeply stained reticulum containing necrotic leukocytes. Epithelial undergrowth appeared then and was further advanced on the seventh day.

The virus used was evidently potent, as large vaccinations, extensive local edema and constitutional symptoms occurred in some cases.

Turnbull and McIntosh described the lesions of the skin in their cases of postvaccinal encephalitis. In these, they saw crusts, including an area of necrotic corium, demarcated by a zone of red cells and broken-down leukocytes. The crusts contained vesicle spaces between the stratum corneum and the stratum lucidum in which were serum and leukocytes. The underlying tissue showed perivascular infiltration with large and small lymphocytes, "hyaline cells," plasma cells, eosinophils and neutrophils. In two cases there were extensive necrosis and exudation of fibrin. Generally there was marked subcutaneous edema.

These changes contrast with those seen by Cory and Unna much as do the lesions produced by viruses obtained by passage through rabbits in those animals with those produced by workers twenty-five years ago with calf virus of that day. The contrast in each instance seems to indicate an enhanced virulence in present vaccine viruses.

Pohl-Pincus inoculated a calf in from twenty to twenty-five places on one side, and from twelve to fourteen days later, on the other side. He excised one or two lesions daily, hardened them in alcohol and studied serial sections stained with methyl violet and picric acid. A line of necrosis appeared along the inoculation wound by the second day, enlarging on the third. Coccus masses were contained in this. The

necrosis did not appear after the second inoculation. The necrosis was surrounded by a zone of "cloudy swelling" with resulting marked thickening of the stratum corneum. In this zone, the nuclei were well preserved or shrunken. To Unna this cloudy swelling appeared to correspond to Weigert's diphtheroid degeneration. Around this was a third zone of "irritation" in which were perinuclear clear zones about shrunken nuclei. This appearance both Pincus and Unna considered artefact, as the latter did not find it after osmic fixation. Widening of intercellular spaces with separation of the cells of the "irritation zone" was seen on the fifth day, and by the eighth day the entire pustule was converted into a necrotic crust surrounded by a zone of "cloudy swelling" and a wide "irritation zone." The period of anemia of the cutis seen by others in smallpox occurred here also.

Touton described the ingrowth of new epidermal tissue under the pustule in the calf, separating it from the pus infiltrated (eitrig) corium.

Kent noted fragmentation of cell nuclei and in the cytoplasm of the cells (epithelial?) the formation of rounded bodies each containing a central hematoxylin stained granule, but gave no details of the histogenesis of the vaccine vesicle.

Copeman and Mann gave a detailed description of the histogenesis of the vaccine vesicle in the calf, paying much attention to the inclusion bodies of Guarnieri. Necrosis and swelling of the basement membrane and profuse emigration of eosinophil leukocytes occurred in the first forty-eight hours. Dilatation of the intercellular lymph channels followed on the third day, then hypertrophy and swelling of the epithelial cells. Next followed reticulation or ballooning. The latter process occurred principally in the lower part of the malpighian layer. In this, the epidermis separated into vertical strands surrounded by lymph. These ruptured, producing intra-epidermal bullae containing free groups of from one to ten cells. Sometimes these isolated balloons swelled to four or five times their original size, forming perinuclear vacuoles and becoming invaded by leukocytes. Karyolysis and a fibrinoid modification of the staining reaction of the cytoplasm followed. Sometimes, on the other hand, the balloons condensed and reacted more like true fibrin. Apparently, these "giant cells" were usually multinucleate. (According to Unna, the balloons of smallpox are more often mononuclear.) Inclusions interpreted as Guarnieri bodies occurred in these. Designated as a third type of giant cell were numbers of vesicular nuclei lying free in cavities among the surrounding cells. At the same time, a process identified with Unna's reticulating colliquation occurred in the upper layers of the rete mucosum. The meshes of the cytoplasmic network became coarser, the intracellular fibers fragmented, and the perinuclear space enlarged greatly. On the fourth and fifth days, necrosis appeared in the basal cells, becoming more extensive and

involving higher layers on the sixth day. In the dermis, edema was seen from the second to the fifth days. At first scanty, later more profuse infiltration with eosinophil and neutrophil leukocytes occurred. On the sixth day, much fragmentation of these leukocytes was seen in dermis and hypodermis. This report of extensive participation of eosinophils in the vaccinia variola reaction I believe to be unique in the literature. These authors did not follow the process beyond the sixth day.

Tyzzer found that vaccination of the skin of a calf produced a picture similar to that of smallpox in man. The primary change was a swelling of the epithelial cells with pallor in staining and the appearance of a reticular structure in the cytoplasm; later vacuolation appeared, and hollowing out of the cell into a clear space containing a shriveled nucleus and bounded by dense adherent cell membranes without prickles. In the developed vesicle, slender trabeculae of epithelial cells passed through its cavity. Multinucleated cells were numerous, containing as many as ten nuclei. Free nuclei were seen in spaces in the epithelium. Numerous cytoplasmic inclusion bodies were seen in epidermal and sebaceous gland cells.

Gailleton first used the rabbit as a vaccinifer, according to Bard and Leclerc. Bard and Leclerc produced pustules on the shaved scarified skin of the rabbit, the contents of which reproduced typical vaccinia in the calf and in a child. The evolution of the pustules proceeded as in the calf. Calmette and Guerin described grossly the evolution of the discrete pustules produced by rubbing vaccine into the shaved, unabraded skin, and noted also the eruption of pustules three or four days later on skin shaved twenty-four hours after intravenous inoculation ("Calmette-Guerin phenomenon").

Tyzzer first reported histologic studies of the lesions of the skin in vaccinia in the rabbit. On the third day, the skin was swollen to two or three times its normal thickness, and the tissue spaces were dilated, containing many polymorphonuclear leukocytes and lymphoid cells. A fibrinopurulent crust covered the surface, and the stratum corneum was swollen and hyaline. In its lower layers, the epithelium showed vacuolar degeneration. Centrally, the spaces were larger, distended with fluid, partly filled with leukocytes and traversed by delicate anastomosing strands; laterally, mitoses were more than usually numerous and many typical vaccine bodies were present. Calf lymph was used in the production of these lesions.

Camus reported the production of pustules of the lips, tongue, buccal and nasal mucosa, nares, conjunctiva, margins of the lids, and anogenital mucosae after intravenous inoculation of rabbits with raw and purified vaccine pulp. These pustules underwent a normal clinical evolution with umbilication. No histologic study was reported.

Levaditi and Nicolau studied the eruption following epilation in a generalized vaccine infection in rabbits. They described formations resembling epithelioma penetrating the derma. These later became swollen and vacuolated. Invasion by migratory elements and separation, vacuolation and necrosis of the epithelial cells followed, resulting in small, later confluent vesicopustules. Watanabe reported a generalized cutaneous eruption in rabbits, with pustules also on lips, tongue and palate. Intravenous inoculations were used. The focal lesions of the skin, examined apparently on the fourth day, showed small round cell infiltrations in the derma, but no epithelial changes.

Ledingham and his co-workers described histologically the lesions produced in the rabbit's skin by fresh calf virus introduced by the dermal, intradermal and intravenous (Calmette-Guerin procedure) methods. In six hours after intradermal inoculation, the corium showed congestion, leukocytosis and polymorphonuclear infiltration. In twenty-four hours, beginning necrosis and phagocytosis by macrophages were evident, and edema appeared in the interpapillary tissue and in the malpighian layer. In forty-eight hours, the corium showed a zone of necrosis containing broken down leukocytes, fibrin and necrotic fibers, walled off by a dense infiltration with polymorphonuclears and some "adventitial cells" (large mononuclears or macrophages?). On the third and fourth days cellular edema and swelling in the malpighian layer appeared, hemorrhages and necrosis of blood vessels occurred in the necrotic area in the corium, and there was proliferation of the "adventitial cells" (fibroblasts?) about the skin muscle. Ballooning is mentioned, but the description does not suggest the process described by Unna under that term. In seven days, the epithelial cells appeared somewhat shrunken and showed mitoses. Organization of the necrotic area appeared and progressed to obliteration of the defect by the fifteenth day. In this process, deeply basophil "plasma cells" formed collagen from their cytoplasm. These "plasma cells" constituted an intermediate phase between the "adventitial cell" and the histiocyte and apparently are not to be identified with Unna's plasma cells. When dermal inoculation was practiced, the epidermal response was more severe, fibrin appearing focally in the malpighian layer. The Calmette-Guerin procedure gave similar lesions. Blocking with india ink produced an enormous hyperplasia of "reticulo-endothelial" elements and an accumulation of ink phagocytes and inhibited the vaccinal reaction.

Sörensen and Sörensen described the lesions of the skin produced in rabbits by calf virus. The epithelium showed intercellular leukocyte infiltration generally and between the mucous and horny layers. When larger quantities of more concentrated lymph were used, there were hemorrhages on and in the skin, and the cellular infiltration and proliferation in the corium were greater. False membranes occurred but were also seen in control material.

Douglas, Smith and Price produced eruptions of the skin by intravenous inoculation of Levaditi's neurovaccine, but gave no histologic description. Bijl and Frenkel described lesions of the skin produced by a neurovaccine. The lesions showed a hemorrhagic tendency, widespread necrosis and marked, sometimes gelatinous, subcutaneous edema at the site of inoculation. Ledingham and Barratt, using a neurovaccine, produced purpuric foci in the skin, which showed massive hemorrhagic necrosis of all tissues down to the skin muscle, without evidence of repair.

Armstrong and I described elsewhere the lesions produced by dermal inoculation and those produced in epilated skin by intravenous inoculation. Armstrong's heat resistant virus was used. In the lesions produced by cutaneous scarification, small vesicular spaces and marked perinuclear vacuolation appeared in the epidermis in forty-eight hours; foci of coagulation necrosis, areas of polymorphonuclear infiltration, numerous clear vesicles with cellular trabeculae and rounded epithelial cells in the cavities and considerable serous exudation in the corium by the third day; more marked polymorphonuclear infiltration in the edematous corium and vesicle spaces, areas of hemorrhage in the corium and beginning subepithelial necrosis by the fourth day; and extension of the partly hemorrhagic necrosis in the corium, in the central part of the overlying epidermis and in the subcutaneous tissue on the fifth day, reaching the cutaneous muscle by the seventh day. From the seventh to the tenth days, the morphologic details in the slough became obscured, and a marginal zone of fibroblast proliferation appeared. At this time, the epidermis still showed marginal, fibrin filled vesicles. Nearby skin showed zones of necrosis surrounding the lymphatic channels.

In the metastatic (Calmette-Guerin) pocks, several varieties of degenerative changes in the epithelium were noted. Earliest was the formation of perinuclear crescentic clefts, which enlarged, becoming circular and showing irregular nuclear shrinkage. Then there were seen areas of intercellular edema proceeding to the formation of wide vesicular spaces with cellular trabeculae irregularly arranged, rounded normal or swollen cells or groups of cells and epithelial giant cells. Other areas showed marked cytoplasmic vacuolation, often combined with the perinuclear cleft formation, proceeding to the formation of a reticulum of condensed cell borders or to transgression of these and the formation of vesicle spaces; irregularly mixed among the last two were groups of large cells with pale-staining cytoplasm gradually giving way to complete liquefaction with accompanying karyolysis; and foci of coagulation necrosis of epithelial cells, occurring in the floors of vesicles, in the upper malpighian layer, in the upper portions of the cellular trabeculae of vesicles and in foci involving the entire thickness of the epidermis. The perinuclear clefts appeared in twenty-four hours, the

large clear cells, the intercellular edema and the patches of edema in the corium in forty-eight hours, small vesicle spaces and areas of coagulation necrosis in three days and invasion of some of the vesicles by large numbers of leukocytes in five days. Further extension and development of these processes followed, but clear vesicles predominated over pustules even to the end of the study, which was terminated at nine days by the death of the last animal. The corium showed edema and hemorrhages as early as the third day; necroses of the glands of the skin and of the connective tissues appeared in five days. Cellular infiltration was at all periods moderate. Polymorphonuclears appeared early, lymphocytes usually predominated, large mononuclear cells of the macrophage type were common, and late and away from the immediate vicinity of epidermal lesions large lymphoid cells of lymphoidocyte type participated to a considerable extent. Unna's plasma cells were rare.

The distribution of the various types of epithelial degeneration was irregular, intracellular vacuolation overlapping the intercellular edema, the clear swelling and the coagulation necrosis, involving also the free rounded cells and cellular trabeculae of the vesicles at times. Usually the various types were fairly well separated and distinct.

These observations appear comparable only with those of Heinrichsdorff in hemorrhagic smallpox.

Summed up, the earliest changes seem to be cell injury in the epithelium, manifested by cytoplasmic and perinuclear vacuolation, cloudy swelling and, in some instances, coagulation necrosis, intercellular edema, vesicle formation, "ballooning" following later and not being seen by all observers. Papillary edema and mononuclear cell infiltration in the corium are seen early. Emigration of polymorphonuclear leukocytes and invasion occur late, except when coagulation necrosis is present; then leukocytes appear earlier. It is notable that coagulation necrosis was seen by Weigert in the severe epidemic of 1870 and 1872, by Heinrichsdorff in hemorrhagic smallpox and by me in the hemorrhagic focal lesions of generalized experimental vaccinia; this change was lacking in the material examined by Buri and by MacCallum and Moody, their material being taken largely during life and at least in part from nonfatal cases. Unna's material, too, I believe, to have been at least partly specimens taken for biopsy. Buri's and Unna's material was collected in the interior of Germany during a period when the mortality from smallpox was very low. Renault and Touton each described coagulation necrosis of the epithelium; there was a pronounced increase in the mortality from smallpox for Paris in the years from 1879 to 1881 (figures for France were not available).[1] Councilman's histologic

1. I am indebted to the comprehensive report of Dr. R. Bruce Low (1918) for the figures on the prevalence and mortality of smallpox.

material all came from fatal cases; his hyaline fibrinoid degeneration includes some coagulation necrosis. On the other hand, the mononuclear cellular reaction in the corium has been stressed particularly by those workers who used material taken for biopsy. Sweitzer and Ikeda especially noted this contrast.

From the foregoing it appears that there may be some direct relation between the virulence of the virus and the amount of coagulation necrosis induced, and possibly a reciprocal relation between these and the amount of mononuclear cellular reaction in the corium.

MUCOUS MEMBRANES

Probably focal lesions of the mucous membranes are next in frequency in smallpox after those of the skin. These have comprised pocks, hemorrhages and more or less widespread diphtheritic inflammatory processes.

Ponfick noted in hemorrhagic smallpox hemorrhages in the mucosa of the upper part of the respiratory tract, particularly that of the nose, in the mucosa of the stomach, colon and rectum, less often in that of the ileum, tubes, uterus and vagina, and commonly in that of the bladder the pelvis of the kidney. There was often also a diphtheritic inflammatory process, especially in the pharynx and larynx. Zuelzer also described hemorrhages in the mucosae of the respiratory and digestive tracts and of the renal pelvis and ureters. Intense diphtheritic inflammation was almost constant on the tonsils, pharynx, upper part of the respiratory tract and female genitalia in his twenty-six cases of hemorrhagic smallpox.

Eppinger stressed the frequency and gravity of lesions of the mucous membranes. Joffroy described a pustular eruption in the larynx and trachea infrequently extending into the primary bronchi and rarely further.

Kendall saw discrete and confluent pustular laryngitides and diphtheritic inflammation; the confluent type showed submucous inflammation.

Breynaert described progressively smaller pustules in the bronchi. These were sometimes umbilicated like the lesions of the skin, but more often were ulcers with slightly overhanging edges.

Huguenin described lesions of the nose, mouth, palate, pharynx, rectum, urethra and vagina.

Roger stated that vesicopustules of the mouth and pharynx developed rapidly and ulcerated early. Hemorrhagic cases showed hemorrhages in the mouth, pharynx and intestine. Pustules were seen also in the larynx, trachea and bronchi, and were often the starting point of a diphtheritic inflammation. He noted otitis clinically in 10 of 755 cases, but no material was examined.

Stokes described dirty, yellowish, false membranes in the larynx and trachea in two of his five autopsies. The epithelium showed granular necrosis without fibrin, with nuclear pyknosis and karyorrhexis. The mucosa (epithelium?) was often raised off the submucosa (corium?) by a serofibrinous exudate. Accumulation of plasma cells, lymphocytes and epithelioid cells was seen in the submucosa (mucosa?). Large numbers of streptococci were seen in the slough and in the vessels.

Perkins and Pay described ulcers in the larynx, trachea (thirty-three cases) and esophagus (five cases) which in early cases resembled skin pocks. Later there was an adherent foul green slough.

Councilman, Magrath and Brinckerhoff described lesions of the soft palate, pharynx, larynx, trachea, cornea (once) stomach (once) and urethra (twice). In these there was first exudation separating the epithelial cells, then hyaline fibrinoid degeneration (cf. Councilman's description of the lesions of the skin) with rounding up and separation of the basal cells, singly or in masses. In this process, the degenerate cells became hyaline and refractile, reacting to Weigert's fibrin stain. Superficial exfoliation followed with resulting denudation of the connective tissue and without formation of vesicles. The connective tissues showed edema, fibrinous exudate and infiltration with polymorphonuclear leukocytes superficially, and deeper with large basophil cells. Some vesicles were formed by total elevation of the epithelium by subepithelial exudation. A variable amount of necrosis of the mucous glands was present. The denuded surfaces showed great masses of streptococci and often a fibrinous false membrane. Cytoplasmic inclusions were seen in the mouth, pharynx and stomach. Purpuric cases showed hemorrhages in the stomach. In purpura variolosa, Riedel saw hemorrhages in the mucous membranes. Heinrichsdorff described the histogenesis of the tracheal lesions in hemorrhagic smallpox (not purpuric). First there appeared necroses in the middle layers of the epithelium; karyorrhexis and invasion by leukocytes ensued, then a breaking down to detritus and leukocytes, often followed by ulceration. The underlying connective tissue contained many lymphoid and plasma cells and small patches of hemorrhage and necrosis in disrupted areas. The capillaries showed hyaline thickening of their walls, endothelial desquamation and probable intracapillary granular thrombi. Sörensen and Sörensen described pharyngeal pocks in three cases. These contained the usual purulent exudate, possessed a keratinized roof, showed septums to some extent and were poorly defined below. Cell inclusions were seen, part taking nuclear dyes, others staining like keratohyalin. Sweitzer and Ikeda and Ikeda reported the presence of hemorrhages in the mucosa of the gastro-intestinal tract in hemorrhagic cases. Edema, congestion and hemorrhagic degeneration of the epithelium occurred, leading to necrosis or exfoliation.

Vaccinia on the tongue in man has been reported in about twelve cases, according to Zurhelle. These have probably been secondary inoculations rather than metastatic lesions. Material for histologic examination does not appear to have been available.

In animals, vaccinal lesions of the mucous membranes have been studied histologically apparently only in rabbits.

Calmette and Guerin produced small vesicopustules in the conjunctiva and nasal mucosa by dusting dried powdered vaccine into these spaces. These evolved in from five to six days and cicatrized without crusting. Immunity resulted in both instances. Histologic examination was not reported. In 1917, Camus described grossly typical pustules of the lips, tongue, buccal mucosa, esophagus (once), nasal mucosa, palpebral conjunctiva, margins of the lids and the anogenital mucosae, resulting from intravenous inoculation with vaccine pulp.

Levaditi and Nicolau described lingual pustules at eight days after intravenous inoculation. In these, the epithelial cells showed swollen vacuolated nuclei, fragmented nucleoli and sometimes total necrosis. There was intercellular polymorphonuclear invasion, forming nests of pus cells. Watanabe described lesions of the lips, palate and tongue in rabbits. These showed intense subepithelial round cell infiltration, distinct swelling of the epithelial cells and areas of elevation of the epithelial layer and vacuole formation; vesiculation, pustulation and ulceration followed rapidly, being completed by the sixth or the seventh day. Gordon, instilling calf lymph into the conjunctivae and nostrils of rabbits, produced a transient conjunctivitis and, nasally, a catarrhal, later purulent rhinitis lasting from the seventh to the tenth day. Immunity was conferred by each of these routes. Lesions of the lips, nose, tongue and palate were produced in rabbits by Douglas, Smith and Price using Levaditi's neurovaccine by various routes of inoculation. These were not described histologically.

Bijl and Frenkel saw ulcers in the esophagus and on the tongue. The epithelium was replaced by "protoplasm" and a mass of nuclear débris, the underlying tissues being infiltrated with leukocytes and proliferating fibroblasts. Toward the margin were seen successively epithelial cells with pyknotic nuclei and highly vacuolated cells containing inclusions stained by hemalum, apparently nuclear fragments. The surface was covered by fibrin, degenerated leukocytes and bacteria. The turbinates were engorged, showing necrosis and necrobiosis of the interstitial tissue and proliferation and necrosis of the epithelium, both diffusely rather than focally. Ledingham and Barratt noted conjunctivitis and pocks on the lips, nose, eyelids, mouth and tongue, but gave no histologic details of these lesions. They also used neurovaccine in rabbits.

Armstrong and I described focal lesions of the turbinate, inner ear, tongue, small and large intestine, trachea and larynx. The material resulted from Armstrong's studies on effects of the heat resistant vaccine virus developed by him. The usual lesion of the turbinate was a focal necrosis showing a sharply defined area of nuclear and cellular débris without marginal reaction in the subepithelial tissue and coagulation necrosis of the epithelium over the center. These necroses sometimes involved the bone and occasionally resulted in complete gangrene of the turbinate. Intra-epithelial, fibrin filled vesicles occurred a few times and contained inclusion bodies in their lateral margins and roofs. The lingual and laryngeal lesions showed marked thickening of the epithelium, centrally coagulation necrosis of the basal cells or even of the entire epithelium, lateral to and above the necrotic cells swollen epithelial cells with perinuclear vacuolation and later multilocular spaces containing greater or less numbers of polymorphonuclear leukocytes. Some lesions of these stratified epithelial mucosae showed separation and rounding up of the basal cells, and the formation of fibrin filled spaces, which sometimes contained multinuclear epithelial giant cells lying free in the space. Some areas of total coagulation necrosis of such epithelia were seen, and in some instances ulcers bounded by necrotic or vacuolated cells occurred. The underlying connective tissue sometimes showed infiltration with lymphocytes and plasma cells, but more often necrosis, with or without polymorphonuclear infiltration. The lesion of the inner ear consisted of focal coagulation necrosis of all structures in an animal that had shown severe antemortem vestibular symptoms. The tracheal lesions showed first epithelial thickening, perinuclear vacuolation in the middle layers, becoming more extensive later, then coagulation necrosis of the entire epithelium. The underlying connective tissue showed fibrinous necrosis, often down to the cartilage, usually without marginal reaction. Epithelial necrosis with or without vacuolation, cell inclusions and stroma necrosis was seen in the few intestinal lesions.

EYE AND LACRIMAL GLAND

Adler saw early conjunctival pustules, and late in the disease a pustular keratitis. He doubted the existence of true corneal pocks. Hebra saw no corneal pocks. Roger, on the other hand, saw frequent severe conjunctivitis and invasion of the cornea, with opacities and perforations, but gave no histologic details.

Councilman and his co-workers saw a corneal pyogenic ulcer once in their fifty-four autopsies on persons who died of smallpox.

The rabbit cornea has been much studied after variolation and vaccination, chiefly in connection with the study of cell inclusions and

in the application of the Paul test for variola. As I have excluded any extensive discussion of cell inclusions from this review because the subject has been so recently covered by Goodpasture, only those papers treating more particularly the histologic changes will be covered.

According to Councilman, the gross changes in the cornea after variolation were first studied by Straus, Chambon and Menard. Guarnieri and Monti, and following them numerous others used the rabbit cornea in the study of the so-called Guarnieri bodies. Tyzzer described the histologic changes following corneal vaccination. After scarification, a thinned layer of epithelium covered the wound in twenty-four hours. Epithelial proliferation and cell swelling followed, increasing the thickness to four or five times the normal. Cell vacuolation was noted on the ninth and eleventh days, but no typical vesicles were formed. The inclusion bodies were seen first after sixteen hours; they became most numerous on the second and third days and thereafter decreased in numbers. Paul, in his original communication on the "Paul test," found a close correspondence of the appearance of the variolated rabbit cornea with Weigert's description of the lesions of the skin in smallpox. There was primary epithelial necrobiosis followed by Unna's ballooning degeneration and reticulating colliquation. Later, small cell infiltration and purulent liquefaction of the pock tissue became apparent. According to Ungermann and Zuelzer, similar changes occur in the variolated guinea-pig cornea. These authors described in detail the changes in the rabbit following corneal variolation and vaccination. In the first twenty-four hours, cellular edema, vacuolation and swelling appeared, even with separation and rounding up of the basal cells. Then numerous mitoses appeared and marked thickening of the epithelium developed. During the second day, necrosis and desquamation of the central swollen cells led to the formation of a crater. In the process of necrosis, the cells rounded up and shrank into dense hyalinized spherules without nuclear staining. Such cells were sometimes engulfed by other epithelial cells, forming the so-called "Schachtelzellen," or "box cells." Giant epithelial cells with multiple heavily stained or pyknotic nuclei in heavily stained cytoplasm appeared within a few hours after inoculation. Leukocyte infiltration of the corneal lamellae appeared after the second day. Marginal epithelial proliferation obliterated the epithelial defect in from six to seven days. The cell inclusions were discussed at length.

Scott and Simon studied the rabbit cornea about forty-eight hours after variolation. They described swelling and hydropic changes of the epithelial cells, central desquamation, "Schachtelzellen" and Guarnieri bodies, but described no ballooning or reticulating colliquation. Douglas, Smith and Price observed conjunctival pocks twice following intravenous inoculation.

Armstrong and I described metastatic corneal and conjunctival lesions seen between the seventh and fifteenth days after vaccination of the skin with his heat selected virus. In the corneal lesions there were epithelial proliferation and thickening, perinuclear cleft formation and cytoplasmic vacuolation, intercellular edema and coagulation necrosis, usually of basal cells, followed by central desquamation and polymorphonuclear infiltration of the edematous superficial lamellae of the cornea, and later more extensive infiltration accompanied by an exudation of serum, fibrin and leukocytes in the anterior chamber. In the conjunctival lesions, actual vesicular spaces were formed. These were traversed by vertical cell cords and showed intercellular edema beneath the lesion and cellular swelling and vacuolation above and laterally. Coagulation necrosis of the basal cells and trabeculae, invasion by leukocytes and superficial erosion followed by the tenth day. Necrosis of connective tissue, infiltration by polymorphonuclears and swelling of capillary endothelium occurred beneath such lesions. Inclusions resembling Guarnieri bodies were seen on the seventh day in both corneal and conjunctival lesions and as late as the eleventh in the corneal lesions.

We also examined lacrimal glands in six animals and found no focal lesions.

While in cases of smallpox corneal and conjunctival material has been but little studied, it appears probable from the extensive work on variolated and vaccinated corneas, and particularly from our account of metastatic corneal lesions that the corneal ulcerations and opacities, as well as the conjunctivitis of smallpox, have been primarily variolous in nature.

LUNGS

Bronchopneumonia has been the most frequent complication of fatal pustular smallpox. Joffroy saw it in about half of his sixty cases, Breynaert in about half of seventy autopsies, Chiari (1886, 1893, in thirty-one of thirty-eight cases, Auché in seventeen of forty-five cases and Perkins and Pay in seventeen of forty-five cases. Councilman, Magrath and Brinckerhoff saw more or less extensive bronchopneumonia in forty-three cases and lobar pneumonia twice in fifty-four cases. Sweitzer and Ikeda stated that bronchopneumonia was the immediate cause of death in their series of cases. Hemorrhages in the lungs in purpuric and hemorrhagic cases have been reported by Zuelzer, Ponfick, Councilman and his co-workers and Ikeda. Bronchitis of greater or less severity has been noted with great frequency (Joffroy, Breynaert, Auché, Huguenin, Roger, Perkins and Pay, Councilman et al., MacCallum and Ikeda). Focal lesions have been described by Ivanowski, Bowen, Bosc,

Stokes and Keysselitz and Mayer. Pustules have been seen in the bronchi by Joffroy, Breynaert, Roger, Perkins and Pay and Councilman et al.

Ivanowski saw in the lower parts of the lung pea-sized red or gray nodules which microscopically showed an alveolar exudate of cells resembling white corpuscles, epithelial cells with cloudy, granular cytoplasm, red corpuscles and a network of fibrous material. In some of these alveoli, he saw fine refractile granules insoluble in acetic acid, caustic alkali or ether and staining light blue or dark red with iodine. The granules were considered parasitic and the nodules as true foci of smallpox. The latter appear to me to have been small bronchopneumonic foci.

Joffroy saw pustules infrequently in the primary bronchi and rarely in smaller ones. He noted bronchitis of greater or less severity in which there was poor epithelial preservation, with marked congestion, little mucus and slight swelling. The pneumonia involved more often the upper posterior parts of the lower lobes and, when unilateral, the right side more frequently than the left. The alveolar exudate consisted of many red corpuscles, even late in the disease, few leukocytes, and deformed desquamated epithelial cells, sometimes with a meshwork of fibrin.

Breynaert (cited after M. Burchardt) saw pustules progressively smaller as the bronchi decreased in caliber. The pustules were sometimes umbilicated, more often appearing as small ulcers with overhanging edges. Bronchitis extended to the finest bronchioles. The pneumonia involved more often the middle parts of the lung, especially on the right. In form there were capillary bronchitis, splenization and splenopneumonia, and confluent, discrete and subacute bronchopneumonia. Histologic details were not given.

Bowen (cited after Chiari) in an 18 days old child dying in the pustular stage noted pneumonia in the right lower lobe, pleurisy on the left and small, sometimes umbilicated nodules in (on?) the lungs, liver and kidneys. These were described as between poppy seed and hempseed size. Structurally, they showed a central network of necrotic cells surrounded successively by zones of infiltration with broken down nuclei and of "exudation." Cocci occurred in colonies in the vessels, but not in the nodules.

Auché described the bronchopneumonia as bilateral, involving more often the lower lobes and the right side. Splenopneumonia occurred eight times, pseudolobar pneumonia five times and nodular bronchopneumonia four times. In the smaller bronchi there were epithelial swelling, proliferation and desquamation and intense infiltration with cells that Auché characterized apparently synonymously in various parts of the paper, as "embryonic" and as round cells. Similar cellular infil-

tration was seen in the adventitial coats of the arterioles. The intimal and muscular layers of these were normal. The bronchial lumen contained chiefly small round cells with small nuclei and much blackish-yellow, granular pigment. In the splenopneumonia, the blood vessels were dilated, and the alveolar "endothelial" cells proliferated and desquamated to form the alveolar exudate. Areas of red hepatization contained a fibrinous intra-alveolar net, "endothelial" cells, white corpuscles and some red cells. In foci of gray hepatization, the alveolar walls were thickened and densely infiltrated by "embryonic cells," their endothelial lining was destroyed and the alveoli were filled by leukocytes and a few large pigment cells. Such foci were often surrounded by zones of splenization and sometimes showed central phlegmonous infiltration. Blood filled alveoli were seen in hemorrhagic foci. The pleura was often infiltrated by leukocytes and occasionally covered by fibrinous exudate. Streptococci, staphylococci and pneumococci were seen in sections and recovered culturally in all combinations, and these cocci were considered to be the cause of the pneumonic complications.

Huguenin (cited after Councilman) referred the bronchitis, capillary bronchitis and telectasis to the specific action of the virus of smallpox.

Roger found that pustules in the trachea and bronchi were often the point of origin of a diphtheritic inflammation.

Bosc saw intense congestion, edema, foci of bronchopneumonia and sometimes ecchymosis. The pneumonic foci he considered microbial in origin. Firm, elastic nodules, from cherry red to dark red, were attributed to the specific action of the virus. These showed proliferation of alveolar and bronchial epithelium and of peribronchial and perivascular connective tissue. On this process, suppuration supervened, and the epithelial cells degenerated and broke down. The nature of these nodules is not clear to me.

Stokes described in one case small vesicles dotting the pleura. Histologically, these showed large lymph spaces filled with serous fluid. Fibrinous pleurisy was seen in another case, and bronchopneumonia in three of five. In two cases, he found foci of necrosis containing, centrally, streptococci and cellular and nuclear débris, bordered by a peripheral zone of proliferated alveolar and endothelial cells, lymphocytes and a few leukocytes.

Perkins and Pay found generally congestion and edema, bronchitis, which was purulent in later cases, bronchopneumonia in over one third of the cases, and fibrinopurulent pleurisy in three of their forty-five cases. Lesions resembling pocks of the skin were seen in the larynx, trachea and bronchi of earlier cases, and ulcers and sloughing later.

According to Councilman, Magrath and Brinckerhoff, the pneumonic exudate contained many polymorphonuclear leukocytes, rare plasma cells, usually little fibrin and commonly streptococci and pneumococci. These

cocci were considered the primary cause of the pneumonic reaction. One of their cases showed focal necroses with cell inclusions in (the epithelium of?) the primary bronchi.

Keysselitz and Mayer found in one case with generalized lesions of the viscera hyperemia of the lung and focal lesions containing free fluid and hemorrhages, but no central necrosis. Guarnieri bodies were seen in both the cytoplasm and the nuclei of fixed and desquamated alveolar epithelial cells. This finding of Guarnieri bodies is unique in smallpox and is paralleled only by the presence of similar inclusions in the alveolar epithelium in the rabbit in the vaccinal pneumonia described by Armstrong and myself and in the focal pulmonary lesions, as well, described by us and by Bijl and Frenkel.

Sörensen and Sörensen described gelatinous pleurisy and hypostatic pneumonia in a case of purpuric smallpox.

Ikeda found marked pulmonary edema and hemorrhage, exfoliation of the epithelium of the smaller bronchi and engorgement and free extravasation of blood in the peribronchial tissues.

Gaucher noted intense congestion but no consolidation in an infant dying fifteen days after vaccination with calf virus and six days after the appearance of a generalized pustular eruption.

Pneumonia has been noted as a complication of postvaccinal encephalitis (Bijl, Turnbull and McIntosh).

Calmette and Guerin, Levaditi and Nicolau and Gordon all practiced intratracheal or intranasal inoculation of rabbits with vaccine virus, producing immunity, but no pulmonary lesions. Levaditi and Nicolau found foci of peribronchial mononuclear and especially polymorphonuclear inflammation, alveolar hemorrhages, edema and atelectasis in rabbits inoculated intravenously with their neurovaccine. Six years later Douglas, Smith and Price reported almost constant production of pulmonary lesions by intravenous inoculation of rabbits with the same virus. These "pocks" in the lung were punctiform hemorrhages, later glistening gray nodules with punctate hemorrhagic centers. Microscopically, these foci resembled "in essentials vaccinial skin lesions."

Bijl and Frenkel produced focal lesions in the lungs of rabbits by cutaneous inoculation with a neurovaccine. Microscopically, pneumonic foci were seen, in which the alveolar septums were so swollen as to obliterate their capillaries. Other foci showed swelling and nuclear fragmentation and pyknosis in the septal cells, both epithelial and endothelial. These cells contained inclusions staining like nuclear material. Sometimes these focal nodules showed coagulation necrosis or necrobiosis. There were rather general hyperemia and desquamation of alveolar epithelium. In bronchi and bronchioles there was often a hyperplastic exudative process with swelling and ulceration of the

bronchial epithelium. The small vessels exhibited intimal swelling, perivascular infiltration with mononuclear cells showing darkly stained nuclei and broad or narrow cytoplasm, and focal swellings of the arterial musculature in which the cells were separated apparently by inflammatory edema. (This appears to be the same as the mucoid degeneration of the arterial musculature in the vaccine virus pneumonia described by us). These authors saw also minute pleural pocks showing thickening or desquamation of the pleural epithelium and subjacent connective tissue, hyalinization and necrosis.

Ledingham and Barratt saw discrete and confluent areas of necrosis of alveolar tissue, with hemorrhage, following inoculation of rabbits with a neurotesticular vaccine by various routes. Vascular and bronchial walls were involved in the necrotic foci. Little evidence of tissue reaction was seen. Subpleural hemorrhagic necroses were covered by lens-shaped areas of pleural epithelial hyperplasia. Another group of animals showed marked proliferation of the "reticulo-endothelial tissue" about the bronchi and vessels and polymorphonuclear infiltration of the focal necroses.

Armstrong and I (1929 and 1930) reported on serofibrinous pneumonia produced by intranasal and intratracheal inoculation of rabbits and on focal pulmonary, pleural, bronchial and vascular lesions produced by the use of other routes of inoculation. We used Armstrong's heat resistant vaccine virus. After intranasal or intratracheal inoculation, epithelial proliferation in the bronchi appeared as early as twenty-four hours, subepithelial necrosis and epithelial desquamation, necrosis and vesicles following on the second day. Focal necroses of alveolar walls and cell inclusions resembling Guarnieri bodies in lesions and in intact bronchial and alveolar epithelia appeared also in forty-eight hours. Gross and microscopic serous alveolar exudation appeared on the second or the third day, and was followed by deposition of fibrin and consolidation on the third or the fourth day. At this time, arterial and venous adventitial edema and necrosis appeared, the arterial musculature became greatly swollen, and this was accompanied by intercellular and intracellular formation of large mucin-filled vacuoles (cf. the "inflammatory oedema" of the muscle noted by Bijl and Frenkel). As the disease progressed, more lobes became involved, first centrally, then throughout; coagulation necrosis and diphtheritic inflammation of the bronchi became more extensive, and necrosis of alveolar walls increased. Death ensued usually in from three to five days, only four of some fifty animals surviving to the sixth, seventh and eighth days. Rapid passage by intratracheal inoculation with raw lung virus produced purulent bronchopneumonia superimposed on the serofibrinous type, but repurification by centrifugation and glycerinization and storage gave a virus that again produced the purely serofibrinous type. About half

the animals inoculated by other routes showed various focal lesions of the lungs, such as smaller or larger foci of serofibrinous pneumonia, bronchial necroses or vesicles and focal necroses of alveolar walls. Serofibrinous pleurisy with or without foci of swollen vacuolated mesothelium occurred in both the pneumonia and the focal lesions.

With the experimental evidence adduced during the past year, particularly the production of a pneumonic process comparable in the lack of leukocytes to the early lesions of the skin in variola, it appears probable that the bronchopneumonia of variola is primarily due to the action of the virus of smallpox, and not primarily to the action of the invading micro-organisms. It is also probable that the latter modify the character of the reaction, the participation of the polymorphonuclear leukocyte in particular being attributable to these cocci.

The perivascular reactions, varying from the proliferative and mononuclear infiltrative type seen by McIntosh and Scarff in vaccinia in rabbits, and the round cell infiltration of Auché in variola, to the necrotizing serofibrinous exudation of Armstrong and myself in the vaccinal pneumonia of rabbits, all appear to constitute a lymphangitis of varying intensity.

HEART AND GREAT BLOOD VESSELS

In hemorrhagic smallpox, myocardial hemorrhages have been noted by Zuelzer, subendocardial hemorrhages by Ikeda, and lesions of the serous membranes, presumably including the pericardium, by Ponfick, Perkins and Pay, Riedel, Sweitzer and Ikeda, and Ikeda. Luksch noted subepicardial hemorrhages in postvaccinal encephalitis.

It is not clear whether the focal lesions observed by Douglas, Smith and Price were myocardial lesions or essentially lesions of the serous membrane, probably the latter, since Armstrong and I also saw focal pericardial lesions in experimental vaccinia. Vegetative endocarditis has been reported once each by Councilman, Magrath and Brinckerhoff in variola and by us in experimental vaccinia of rabbits, Interstitial myocardial infiltration with "large basophilic cells" was seen four times in the series of Councilman and his co-workers, and lymphocyte infiltration and fibroblast proliferation once in our rabbits with vaccinia. Cloudy swelling of heart muscle has been generally observed in variola and also in experimental vaccinia by us. More severe degenerative changes, even necrosis, were occasionally seen, but it appears that the necrosis, at least, was associated with streptococcal emboli (Councilman).

No lesions of the great vessels attributable to the action of the virus appear to have been observed either in vaccinia or variola, though these are specifically mentioned only in the studies of Councilman and his co-workers in variola and ours in vaccinia.

LIVER

In smallpox, hemorrhages in the parenchyma of the liver have been noted by Wagner and Roger, subcapsular hemorrhages by Keysselitz and Mayer and Ikeda. According to Councilman, Quinquaud first observed lobular foci of hepatitis and fatty degeneration of the cells. Curschmann saw cloudy swelling of the liver cells and severe fatty degeneration comparable to that of phosphorus poisoning.

Weigert first described what he designated as bacterial thrombi in the sinusoids of the liver. Stained with hematoxylin, carmine and picric acid, these were hematoxylin staining masses of granular material. The surrounding tissue cells were often normal; at other times, they showed karyolysis and complete loss of nuclear staining. These microscopic focal necroses did not exceed the size of small tubercles. Later, the central bacterial thrombi lost their definition, the cell bodies broke down to masses of débris, forming round, sharply defined patches without nuclei and without marginal reaction. In the later stages, the margins were made up of smaller liver cells with more numerous nuclei.

Barthélemy noted extensive fatty degeneration in nineteen of twenty-three cases. Sireday noted lesions of the interstitial tissue and cloudy swelling of liver cells in early cases; later there was fatty degeneration of all parts of the lobule. Bowen described nodules varying in size from that of a poppy seed to that of a hemp seed, partly umbilicated, on the liver, lungs and kidneys. In these there was a central network of necrotic cells surrounded by a zone densely infiltrated with fragmented nuclei, and peripherally by a zone of "exudation." The foci contained no bacteria, but coccus colonies occurred in the vessels of these organs.

Arnaud (1899) saw varying degrees of fatty infiltration of the liver cells, more marked toward the periportal areas. Nuclei were usually preserved. Less often there was granular degeneration with vitrification of the cytoplasm and disappearance of the nucleus of the liver cell, whether in isolated cells or in focal areas is not clear. There was dense "embryonic" infiltration of the periportal and interlobular connective tissue with small round cells. Small round cell infiltration of the walls of the larger blood vessels and endothelial proliferation and swelling in the smaller vessels were noted. There were vascular stasis and marked intracapillary leukocytosis, including lymphocytes, polymorphonuclears, phagocytes and lymphoid cells in mitosis. Roger and Garnier (1901) and Roger described the liver in smallpox with great detail. The organ was enlarged, soft, pale yellowish and greasy. Periportal round cell infiltration was seen in some cases. Capillaries and veins showed dilatation, sometimes with endothelial swelling and desquamation. In the liver cells, the most frequent change was fatty degenera-

tion, usually without loss of nuclear staining; this change was more pronounced in the periportal regions. Also there were foci of a few swollen cells with broad clear cytoplasm and poorly stained nuclei. In some cases there were foci of necrosis and "vitreous degeneration" in which there were shrunken cells with poorly stained nuclei or none at all. Such foci lay in the midst of well preserved liver tissue. They were often invaded by leukocytes, and not infrequently central caseation had occurred. Some cases showed complete disassociation of the liver cell cords, leaving free, rounded cells.

Bosc described fatty degeneration in what appears to have been a cirrhotic liver, ascribing all the changes to smallpox. Stokes saw cloudy swelling in all cases. In one there were focal necroses containing, centrally, nuclear débris and homogeneous eosinophilic material, and marginally, coalescing liver cells with fragmented nuclei. The focal lesions contained no streptococci, though these were numerous elsewhere in the capillaries. Perkins and Pay saw central passive congestion and peripheral fatty degeneration of the lobules in twenty-three of their forty-five cases.

Councilman, Magrath and Brinckerhoff found regularly a great increase in the weight of the liver, general swelling and increased granularity of the liver cells. In seven cases, the liver cell cords were disassociated into separated cells lying free in the stroma. In six there were foci of small eosinophilic necrotic liver cells without nuclei, with dilated capillary spaces, and in four with invasion by polymorphonuclear leukocytes. In three autopsies they observed scattered, isolated necrotic liver cells. In other cases there were nuclei with centrally clumped, more or less oxyphil chromatin and swollen karyolytic nuclei, with or without cytoplasmic degeneration. The capillaries often contained pyogenic cocci and, late in the disease, numerous "large basophile cells." In five cases, refractile, hyaline, eosinophil bodies were seen lying in vacuoles in the liver cells, more often nearer the centers of the lobules.

Keysselitz and Mayer described focal lesions of variable size in the liver in two of their three cases. The larger ones involved several lobules; the smaller occurred in all parts of the lobules. In them were clear fluid with or without red corpuscles, a few polymorphonuclears and rare eosinophils and mononuclears, and nonnucleate masses arising from liver cells, gradually merging into opaque coagulated masses and granular débris. Peripheral to these areas of necrosis were necrobiotic liver cells with swollen clear nuclei, patches of intercellular edema and dilated capillaries. Cell inclusions ranging from eight microns down in size and staining like nucleolar material occurred chiefly in the cytoplasm of liver cells, but also in their nuclei, which sometimes contained at the same time an intact nucleolus.

MacCallum described marked enlargement, intense cloudy swelling and occasionally focal necroses in the liver. Ikeda described slight cloudy swelling of the liver in purpura variolosa. There were numerous wandering mononuclears (which are marked "lymphocytes" in his illustration) between the liver cell cords and in the periportal spaces.

In fatal generalized vaccinia in an infant, Gaucher saw flecking of the liver by foci of fatty degeneration. The infant died on the sixth day of a generalized pustular eruption and fifteen after vaccination with calf virus. Turnbull and McIntosh saw congestion and parenchymatous degeneration of the liver in their cases of postvaccinal encephalitis. In one case there were focal necroses, which were unfortunately not studied histologically.

In experimental vaccinia of rabbits, small inflammatory foci containing degenerated polymorphonuclear leukocytes were observed by Levaditi and Nicolau. Douglas, Smith and Price saw focal lesions of the liver in about two thirds of their animals, omitting those which had received the rapidly fatal intracerebral inoculations. The lesions in the livers were examined for them by Turnbull and were said to resemble "in essentials vaccinial skin lesions." After noting the extreme pleomorphism of the cutaneous lesions produced in rabbits by a virulent vaccine virus, I find it rather difficult to imagine the appearance of such lesions within a parenchymatous organ. I strongly suspect that most of the lesions attributed by these workers to the viscera were in fact lesions of the serous membrane on their surfaces.

Bijl and Frenkel described diffuse endothelial proliferation and increased numbers of various leukocytes in the capillaries of the liver, reminding them of a leukopoietic process. The cell types were insufficiently described or named to permit identification of the process. Necrosis was present under the capsular lesions, which will be discussed under peritoneum.

Ledingham and Barratt saw multiple focal necroses of liver cells, usually with initial hemorrhage. These foci were rapidly replaced by bile duct proliferation in rabbits from nine to twelve days after inoculation. Fibrosing granulomas were interpreted as probably coccidial in origin, an interpretation in which I concur.

Armstrong and I found focal necroses in 54 of 124 rabbits inoculated by various routes with his heat selected vaccine virus. The incidence of these was much higher when the rapidly fatal intracerebral and respiratory infections were eliminated. The size of the lesions varied from those involving isolated cells to those involving two or three lobules. There were first increased cytoplasmic oxyphilia and pyknosis or karyolysis, then swelling and vacuolation of the liver cells, disappearance or fragmentation of their nuclei, occlusion of the capillaries by the swollen

cells and fine fibrin thrombi. In apparently later lesions, the liver cells were shrunken, often broken down to granular débris and free fat, and sometimes infiltrated with leukocytes. Calcification was seen in some late lesions and in others marginal endothelial proliferation, gradually changing into nodules of epithelioid cells. The bile duct proliferation noted by Ledingham and Barratt was seen in this material, too, and was attributed rather to the common proliferative chronic cholangeitis often seen in rabbits.

The focal necroses described by Weigert, Bowen, Stokes, Councilman and his co-workers and Keysselitz and Mayer, the foci of "vitreous degeneration" of Arnaud, the vitreous degeneration and necrosis of Roger and Garner in smallpox and the focal necroses seen by Ledingham and Barratt and by us in vaccinia in rabbits appear to represent essentially the same process. That the lesions seen by Turnbull and McIntosh in postvaccinal encephalitis and by Douglas and his co-workers in vaccinia in rabbits are similar seems probable. The hematoxylin-staining granular masses interpreted by Weigert as bacterial thrombi lying in the centers of the focal lesions have not been seen since in either variola or experimental vaccinia. I am somewhat inclined to doubt their bacterial nature.

PANCREAS

This organ was specifically mentioned only by Stokes, Perkins and Pay and Councilman, Magrath and Brinckerhoff in reports on variola and by us in reports on experimental vaccinia. No lesions attributable to the virus were found by any of these writers.

PERITONEUM

In hemorrhagic and purpuric smallpox, peritoneal hemorrhages have been described frequently by Zuelzer, Councilman and his co-workers, Riedel, Sweitzer and Ikeda and Ikeda. According to Chiari, pustules, in part umbilicated, were seen by Gosselin on the tunica vaginalis testis. This observation appears to be unique in variola. Local peritonitis was seen in one of Turnbull and McIntosh's cases of postvaccinal encephalitis with ulceration of the bladder.

In rabbits, Ledingham produced subperitoneal nodules with small central necroses, using intrasplenic and intraperitoneal inoculations of fresh calf virus. The central necroses were surrounded by "adventitia cell" proliferation like that in the lesions of the skin. Douglas, Smith and Price, using a neurovaccine, produced frequent peritoneal lesions by intraperitoneal and intratesticular inoculation, rarely by other routes. There was a clear, yellow, gelatinous exudate with small white or hemorrhagic peritoneal spots on the surfaces of the organs, which microscopically resembled "pocks in the earliest stages."

Bijl and Frenkel saw in several of their vaccinated rabbits rounded, white, often umbilicated lesions on the capsules of the spleen and liver. These showed capsular thickening, swelling and hyalinization of the fibers just beneath the surface and necrosis with nuclear débris beneath (or among? "unter") these.

Ledingham and Barratt saw gray papules on the intestine in one rabbit. These showed necrosis in the serosa and great hyperplasia and numerous mitoses in the serous endothelium. Similar lesions were seen on the surfaces of the uterus and ovary. Neurovaccine was used.

We described two types of serosal lesions produced by the heat selected vaccine virus. The first was focal necrosis of the serosal connective tissues. This was sharply defined, containing cellular and nuclear débris centrally, without marginal reaction. In the second type, the mesothelium was thickened, its cells separated by serofibrinous exudate, forming simple or septate vesicular spaces. Coagulation necrosis of some of the mesothelial cells was seen, usually below the surface layer. Necrosis and less often infiltration by leukocytes and proliferation of fibroblasts were seen in the underlying connective tissue.

While a part of the peritoneal lesions seen by these workers were undoubtedly due to direct peritoneal contamination, others were just as surely metastatic. Gosselin's pocks were probably of the same nature as the experimental lesions. Further study of the latter is needed, as Armstrong and I, who had the largest experimental material, studied only six cases with the vesicle-like lesions.

SPLEEN

Wagner noted splenic infarcts in hemorrhagic smallpox. Zuelzer and Ponfick did not see splenic enlargement in hemorrhagic cases, Golgi found the spleen small, dark and hard, while Birch-Hirschfeld described enlargement. Roger stated that the spleen was less often enlarged than in pustular cases. Arnaud (1899) noted no significant difference in splenic size between hemorrhagic and pustular smallpox. He saw enlargement of the malpighian corpuscles and hemorrhages in the pulp. Such hemorrhages were reported in hemorrhagic smallpox also by Perkins and Pay and by Councilman, Magrath and Brinckerhoff. Riedel stated that the spleen was small.

Weigert found focal necroses with central bacterial masses. As the necrosis advanced to the stage of central débris without nuclei, the central masses of bacteria disappeared. In pustular smallpox, Arnaud (1898b) saw frequent enlargement of the splenic corpuscles and multiplication of their cells. Congestion of the pulp was common; foci of mononuclear and lobate leukocytes were seen, and there were moderate numbers of large mononuclear cells, a few large swollen cells occa-

sionally containing red cells, and numerous small lymphocytes, these last filling the pulp spaces and infiltrating the splenic connective tissue and blood vessel sheaths. Roger described splenic enlargement in pustular cases. The pulp contained a few megakaryocytes and plasma cells, and numerous mononuclear, nongranular and neutrophil cells. Stokes saw no significant changes. The spleen was enlarged in about half the cases described by Perkins and Pay. The splenic corpuscles were generally enlarged. The pulp contained numbers of phagocytic cells including red cells and nuclear débris. Three of their pustular cases showed hemorrhages in the pulp.

Councilman, Magrath and Brinckerhoff stressed the paucity of polymorphonuclear leukocytes before the stage of desquamation and emphasized the prominence of proliferating large basophil cells, in both follicles and pulp. The reticulum contained many large phagocytic cells including nuclear débris from lymphocytes. Some of these cells showed inclusion bodies. Pulp hemorrhages were frequent, and fibrin deposition in pulp spaces and sinuses occurred. In late cases, pigment was present in considerable amounts. Keysselitz and Mayer found focal lesions in the spleen like those described by Weigert. They also described numerous intranuclear inclusion bodies in vascular endothelial nuclei, which showed peripheral chromatin condensation and clear centers.

In their cases of postvaccinal encephalitis, Turnbull and McIntosh described inflammation of the spleen. Four cases showed increase of polymorphonuclears and five increase of basophil mononuclears. Early central necrosis of the splenic corpuscles was seen in one case.

In experimental vaccinia of rabbits, no lesions were seen by Levaditi and Nicolau. Douglas, Smith and Price frequently saw white spots on the surface of the spleen, which were later slightly sunken and showed a grayish translucent zone. Though no specific histologic description was given, these would appear to have been peritoneal or capsular lesions rather than lesions of the splenic parenchyma. Bijl and Frenkel saw no parenchymatous focal lesions. They described capsular lesions which I have discussed under peritoneal lesions. They described hyperemia of the pulp, hypertrophic changes in the follicular reticuloendothelium, sometimes with nuclear fragmentation, and much nuclear detritus and hemosiderin in the pulp. Isolated focal necroses in the splenic pulp of the rabbit were first described by Ledingham and Barratt, who saw them in one case only. Such lesions were found by us in 6 of 113 rabbits. In these, the cells were strongly oxyphil, with karyorrhexis, pyknosis or karyolysis, and later, caseous débris. Hemorrhage and deposition of fibrin were each sometimes seen within and in the margins of the lesions. The marginal reticulum cells sometimes showed nuclear swelling and karyolysis; no other marginal reaction was

evident. We also noted small hyaline thrombi in the splenic pulp. Leukocytosis, follicular hyperplasia, hyperemia, hemosiderosis and much nuclear débris in phagocytes were noted in many animals, but only in a minority in each instance.

Summarizing, one finds that there has been much disagreement as to the size of the spleen, diffuse cellular changes and follicular hypertrophy, and it appears probable that these changes have been dependent in large measure on factors other than the virus of variola and vaccinia. The cell inclusions described by Councilman and his co-workers and Keysselitz and Mayer may be specific, but this appears dubious to me. The focal necroses described by Weigert and Keysselitz and Mayer in variola and by Ledingham and Barratt and by Armstrong and me in experimental vaccinia appear to be specific and due to the virus.

BONE-MARROW

Golgi first examined the bone-marrow in smallpox, noting a predominance of red corpuscles in the hemorrhagic forms and of white corpuscles in the pustular cases. Osteomyelitis variolosa was first described by Chiari (1893) and further studied by Mallory (1894) while working in Chiari's laboratory. In this there were yellowish focal lesions of the size of a split pea or less, with a red areola. The foci were composed of large epithelium-like marrow cells with pale nuclei and fat droplets in their broad cytoplasm. In the prepustular stage, central necrosis and peripheral fibrin and edema appeared. Later, necrosis involved most of the "epithelioid" cells and also the bone cells of any included bone trabeculae. No appreciable emigration of or infiltration with leukocytes occurred. Such lesions occurred in twenty of Chiari's twenty-four cases; Mallory on more extended search found them regularly.

No focal lesions were seen by Roger. Nongranular, eosinophil and neutrophil cells predominated; polymorphonuclears, plasma cells and megakaryocytes were rare. Infants with bronchopneumonia showed hyperplasia corresponding to the leukocytosis. Muir saw almost complete absence of polymorphonuclear leukocytes, reduction in myelocytes and vascular dilatation in the rib marrow. Chiari's osteomyelitis variolosa was not found.

Councilman, Magrath and Brinckerhoff saw focal necroses of variable size, often hemorrhagic, and without marginal reaction. Hemorrhagic and other early cases showed extensive diffuse and focal degeneration. Exudation of fibrin occurred in and near areas of hemorrhage and necrosis and elsewhere. Large phagocytic cells were seen including other cells and absorbing fat. In general there was a great reduction in polymorphonuclear leukocytes and an increase in lymphoid and plasma

cells. Keysselitz and Mayer saw, but did not specifically describe focal lesions in the bone-marrow. Batzdorff described a suppurative osteomyelitis in material removed surgically seven weeks after variola. Musgrave, Sison and Crowell described histologically healed lesions in the bones of a patient who had had smallpox in childhood. They also studied in living patients, bony deformities, which they attributed to past smallpox. Brown and Brown found metastatic pyogenic osteomyelitis the most commonly reported variety in the literature. On x-ray and clinical evidence, they believed Chiari's osteomyelitis variolosa to have been the cause of bony deformities in their two cases.

MacCallum described nodules showing central necrosis of marrow cells and marginal infiltration by mononuclears. Formation of polymorphonuclear leukocytes was suppressed and many degenerate leukocytes were seen.

Sweitzer and Ikeda saw red marrow in the femur frequently in purpura variolosa, and Ikeda described hemorrhages with islets of normoblasts and a few myeloid cells.

Soltmann reported what he designated as "osteomyelitis ichorrhämica" in a child dying thirteen days after vaccination and three days after the onset of symptoms. Limited autopsy showed necrosis of the anterior surface of the femur, with edema and yellowish muscles above it. The marrow cavity was not opened. The etiology was considered uncertain.

In experimental vaccinia in rabbits, Levaditi and Nicolau saw no lesions of the bone-marrow. Bijl and Frenkel saw marked proliferation of myelocytes, hyperemia, a diffuse fibrin network and scattered small regressive changes, which were not further characterized. We saw focal necroses of the bone-marrow of the femur or diploë in five of twenty-six rabbits. These showed, centrally, fragmented cells and nuclei surrounded by a zone of empty reticulum, or central caseous necrosis surrounded by fat-containing, coagulated, granular myelocytes with karyolyzed or pyknotic nuclei. Exudation of fibrin and hemorrhage occurred in such lesions, and fibrin was seen in patches where scattered cells showed fragmented or pyknotic nuclei. Direct intramedullary inoculation produced similar, but larger areas of coagulation necrosis. Bone lying in foci of necrosis showed necrotic bone cells.

To date, the osteomyelitis variolosa of Chiari has been studied histologically by Chiari, Mallory, Councilman and his co-workers, Keysselitz and Mayer and MacCallum in variola and by us in experimental vaccinia. Probably the report of Bijl and Frenkel could be included, but the description is not clear. This osteomyelitis appears to be a specific effect of the virus. The suppression of polymorphonuclear leukopoiesis seems to have been quite generally observed, though we saw

an increased number of polymorphonuclears in ten of twenty-six animals in experimental vaccinia.

LYMPH GLANDS

Wagner saw hypertrophy and hyperemia of the lymph nodes. Weigert described his bacterial thrombi in the follicles and peripheral sinuses of lymph nodes, and apparently included these organs in his description of focal necroses, which applied more specifically to the liver, spleen and kidney. Roger described frequent enlargement of the lymph nodes in smallpox. The pulp cords showed neutrophil, basophil and sometimes eosinophil myelocytes, giant cells of undescribed type and, in hemorrhagic cases, nucleated red cells as well. Similar active myelopoiesis occurred in the periglandular tissue. These most interesting changes Roger had not seen except in variola, and unfortunately he does not state in how many cases these changes occurred. They have never been confirmed.

Stokes found extensive focal necroses in the bronchial and cervical lymph nodes, usually subcapsular and often containing large masses of streptococci. Councilman, Magrath and Brinckerhoff observed edema, dilatation of the peripheral sinuses, multiplication of large basophil cells by mitosis, these often taking on the characteristics of Unna's plasma cells, and evident proliferation of sinus endothelia to form large free phagocytic cells containing cells, débris and masses of fibrin. There were frequent degeneration and necrosis of small cells (whether focally or diffusely is not stated). Mononuclear eosinophils were frequent, polymorphonuclear eosinophils less so. In late stages, polymorphonuclear leukocytes became numerous. Cocci were frequent in some cases. MacCallum saw many large phagocytic cells in the lymph sinuses, also abundant smaller mononuclear cells. Sweitzer and Ikeda described inconstant adenopathy, intense hyperemia and diffuse hyperplasia of the lymphoid cells.

According to Turnbull and McIntosh, the axillary lymph glands draining the area of the vaccination in postvaccinal encephalitis were enlarged and congested, showing free blood in the sinuses in three, and hemorrhages in two of the seven cases. There was some eosinophil infiltration.

In experimental vaccinia, Bijl and Frenkel saw swelling and degeneration of the sometimes phagocytic reticulo-endothelium of the peripheral and medullary sinuses and germinal centers. There were scattered small necroses and hemorrhages. Armstrong and I (1929 and 1930) saw in the mediastinal glands in pneumonic cases and in axillary glands after cutaneous inoculation with the heat selected vaccine virus, first, edema and exudation of fibrin in the sinuses, then

coagulation necrosis, first of the peripheral sinuses, later of the entire gland. Such necroses were often hemorrhagic.

In general, the lymphadenitis of variola and vaccinia shows a mononuclear cell response. With some strains of virus, hemorrhage and necrosis overshadow and obliterate the reaction. Such strains are those which show the greatest necrotizing tendencies in the skin and other organs.

THYMUS

Focal lesions of the thymus have been noted only by Armstrong and me, in a rabbit inoculated cutaneously with the heat selected vaccine virus. The lesions were multiple focal hemorrhages and areas of necrosis in which the reticulum cells appeared to survive, and the lymphocytes were replaced by nuclear débris and fibrin. No marginal reaction occurred.

SUPRARENAL GLANDS

Oppenheim and Loeper first described the occurrence in the suprarenal gland in smallpox, of foci of infiltration with lymphocytes and fewer plasma cells, most often in the medulla, about the sheaths of the central veins and also sometimes in the capsule. There was also rarely congestion, with hemorrhage and "cellular necrosis in islets." The last observation was, unfortunately, not more closely described. Stokes saw no significant changes. Perkins and Pay found cystic suprarenal glands in six of forty-five cases and noted frequent fatty degeneration of the medulla.

Councilman, Magrath and Brinckerhoff saw foci of necrosis in some cases, and more or less degeneration in more. The foci showed increasingly oxyphil, vacuolated cytoplasm with droplets of hyaline material and karyolysis, in some instances with cytoplasmic disintegration. There were also small foci of infiltration with large basophil cells, chiefly in the medulla.

In experimental vaccinia, Levaditi and Nicolau described the suprarenal glands of their rabbits as "en apparence non lésé." Douglas, Smith and Price saw in twenty rabbits focal lesions which they described as "pocks" or as resembling small accessory suprarenal glands. Possibly they referred to peritoneal lesions overlying the suprarenal glands; certainly, these were not the same as the lesions described by Bijl and Frenkel, Ledingham and Barratt and us. Bijl and Frenkel described focal coagulation necroses containing, centrally, an eosinophil mass with nuclear fragments, and peripherally, necrobiotic epithelial cells and much nuclear débris, which was presumed to originate, at least in part, from leukocytes. "Corpuscular elements" were seen in the cytoplasm of cells in the marginal zone. Around this was a zone of capillary endothelial proliferation and probably some leukocyte infil-

tration, with some cells resembling nucleated red cells, which the authors would derive from the capillary endothelia. Beginning calcification was noted in the necrotic centers. Capsular lesions of the same type as seen on the liver and spleen were noted; these I have discussed under peritoneum. Whether the cytoplasmic "corpuscular elements" referred to were inclusion bodies in the sense of Guarnieri bodies is not certain from the text.

Ledingham and Barratt found cortical focal necroses almost constantly. These were hemorrhagic in the earlier stages, and later showed a marginal "reticulo-endothelial" reaction consisting of plasmacytoid adventitial cells. Polymorphonuclear invasion of the necroses was seen in one rabbit. We saw frequent focal necroses, usually after the fourth day. First there were swelling, increased vacuolation and loss of lipoid and cytoplasmic oxyphilia in the cortical cells. Soon afterward pyknosis, karyorrhexis or karyolysis, and the intercellular deposition of a fibrin net appeared, followed by a central breaking down to caseous débris; a marginal zone of swelling of cells and vacuolation still remained in some instances. Marginal or central hemorrhage was frequent. In some late lesions there was central calcification; in others, moderate invasion by polymorphonuclears; in others, marginal proliferation of fibroblasts proceeding to the formation of small granulomatoid foci; in still others there was marginally active multiplication of small, otherwise typical cortical cells, sometimes mixed with lymphocytes. Such lesions were found in 62 of 118 animals. There were also occasional areas of small round cells in the medulla, the significance of which appeared uncertain.

That the foci seen in smallpox by Oppenheim and Loeper and by Councilman and his co-workers are the same as those seen by Bijl and Frenkel, Ledingham and Barratt and Armstrong and myself appears highly probable.

KIDNEY

In hemorrhagic smallpox, hemorrhages in the pelvic and ureteral mucosae have been reported by Zuelzer, Ponfick, Unruh, Roger, Perkins and Pay, and Councilman, Magrath and Brinckerhoff; parenchymatous hemorrhages by Roger, and subcapsular hemorrhages by Roger and by Ikeda.

Weigert saw his bacterial thrombi in the glomeruli, cortex and medulla, but, as nearly as I can discern, the focal necroses that he described as found in the liver and spleen did not occur in the kidney. Bowen described poppy seed to hemp seed sized nodules in the lungs, liver and kidneys in a case of pustular smallpox. In these there was a central network of necrotic cells, a margin of nuclear fragments and a peripheral zone of "exudation." Arnaud (1898a,b) described exten-

sive interstitial infiltration with "lymphatic cells" and proliferation of "embryonic" connective tissue, swelling of glomerular capsular epithelium, more or less marked swelling and granular, fatty or reticular degeneration of the convoluted tubules, rarely hyaline degeneration and necrosis, occasionally arteriolar thrombi and in one case exudative glomerulitis. Huguenin saw cloudy swelling and frequent glomerular involvements. Roger noted a great similarity to the nephritis of scarlet fever. Stokes also saw in one case an acute interstitial nephritis like that of scarlet fever, plasma cells and lymphocytes forming the exudate. Another case showed hyaline glomerular degeneration, capsular epithelial proliferation and general granular, fibrinoid and fatty degeneration of the tubules. Perkins and Pay saw one case of acute interstitial nephritis, the exudate being plasma cells, eosinophils and a few polymorphonuclears. More or less extensive chronic nephritis was seen in one fourth of the remaining cases.

Councilman, Magrath and Brinckerhoff saw constantly more or less acute degeneration, chiefly in the convoluted tubules, and frequent focal interstitial and intravascular accumulations of lymphoid and large basophil cells. Streptococci were frequent; leukocytes were almost absent. Acute glomerulonephritis was seen in five cases, and acute suppurative nephritis in two. One purpuric case showed a considerable amount of necrosis in the foci of mononuclear cells. Keysselitz and Mayer described focal coagulation necroses with central caseation and marginal degeneration and with Guarnieri bodies in the renal epithelium in one case. Their other cases showed severe parenchymatous degeneration to the extent of necrosis in parts, but no inclusions. MacCallum described degeneration of the tubular epithelium, occasional glomerulonephritis and frequent interstitial infiltration by mononuclear cells.

The case reported by Russell and Oddie as postvaccinal encephalitis gave no anatomic evidence of that condition, but did show tubular degeneration with slight deposition of calcium, glomerular swelling and nuclear multiplication, which taken with the pronounced nitrogen retention recorded indicated a nephrosis the connection of which with the preceding vaccination is at least uncertain.

No focal lesions of the kidneys of rabbits in experimental vaccinia were reported by Levaditi and Nicolau, Douglas, Smith and Price, Bijl and Frenkel, Ledingham and Barratt or Armstrong and myself. We saw more or less severe degenerative changes in the convoluted tubules, albuminous and fibrinoid casts in some and old fibrous scars with tubular atrophy in several, often associated with areas of infiltration by lymphocytes. Walthard (1927) inoculated a rabbit intrarenally, producing hyperemia, tubular swelling and patches of infiltration with leukocytes and lymphocytes at the site of inoculation.

Focal necroses of the kidney have been reported apparently only in the single cases of Bowen and of Keysselitz and Mayer; hence it is not surprising that they have not been encountered in the experimental disease. The most constant feature appears to have been the rather severe tubular degeneration. Interstitial infiltration by mononuclear cells has been frequent. While Armstrong and I have seen this in rabbits also, in this animal its significance is less clear, owing to the relative lack of familiarity with the histogenesis of the chronic focal scarring often seen in the rabbit.

MUSCLES AND FASCIAE

Zuelzer noted hemorrhages in the voluntary muscles and large nerve sheaths in hemorrhagic smallpox. Ponfick saw hemorrhages in the connective tissue generally. Stokes saw no significant changes in the muscles. In experimental vaccinia, Douglas, Smith and Price saw, but did not specifically describe, focal lesions in the voluntary muscles and in the connective tissues. In experimental vaccinia of rabbits, Bijl and Frenkel saw coagulation necroses of voluntary muscle with karyorrhexis, loss of striation and calcification. Aside from the coagulation necrosis of the platysma, which I have mentioned in consideration of cutaneous vaccinations, Armstrong and I saw granular, waxy and fragmentary degeneration in the voluntary muscles, but encountered no focal lesions. Extensive edema and multiple focal hemorrhagic necroses in the deep fascia of the legs occurred once after intravenous inoculation.

TESTIS

I am indebted to Chiari for many of the older references in regard to lesions of the testes. Pustules on the tunica vaginalis testis, in part umbilicated, were seen by Gosselin. Serofibrinous inflammation of the tunica vaginalis was seen frequently by Béraud and Robin. Béraud first described multiple yellowish foci in the parenchyma of the testis. These lesions varied from the size of a pea to that of a pinhead. In these, the tubules were swollen and showed albuminous degeneration. Pus cells were lacking. In hemorrhagic smallpox, Wagner saw grayish-red, later yellowish, small, new formations in the testicular parenchyma. These foci were generally lymphatic. Zuelzer, in hemorrhagic smallpox, simply referred to hemorrhages in male and female generative organs. Laboulbéne noted serofibrinous periorchitis, and in both testes minute hemorrhages and small yellowish-red foci showing central nuclear and cellular albuminous degeneration, surrounded by a zone of purulent infiltration. Géraud saw bilateral orchitis following revaccination of two soldiers.

Chiari found, chiefly in boys but also in adults dying of smallpox, multiple grayish-yellow nodules in the testicular parenchyma. These were pea-sized, sometimes bloodstained, later hard and dry. In the earlier stages, these showed focal interstitial swelling, small cell infiltration and necrosis, with well preserved or degenerate but not necrotic tubules included. Later, in the stage of exsiccation, the tubules also necrosed, the centers became homogeneous, the peripheral zone of small cell infiltration narrowed, and coagulated exudate appeared in the surrounding interstitial tissue. Chiari, in 1886, first suggested the testicle as a source of uncontaminated smallpox virus. Roger found lymphocyte and mononuclear exudate in the tunica and intense congestion and infiltration of the interstitial tissue of the testis, but no focal necroses. This infiltration consisted of a fibrin net, numerous mononuclears and small hemorrhages. Degeneration of the tubules varied between aspermatogenesis and necrosis. Stokes saw necroses beginning in the tubular epithelium, accompanied by thickening and later necrosis of the interstitial supporting tissue, including even the arteries. Perkins and Pay described focal necroses of the testes in eight of twenty-seven cases. In these, the interstitial tissue was infiltrated and the tubules necrotic. Bacteria were frequent in the vessels, and streptococcal thrombi were seen in arterioles.

Councilman, Magrath and Brinckerhoff saw no focal necroses, but noted numerous foci of infiltration with lymphoid and large basophil cells in the interstitial tissue, often with hyperemia, hemorrhage and a little exudation of fibrin. Tubular necrosis and invasion by phagocytes sometimes occurred in larger foci. Polymorphonuclear leukocytes were absent. More or less tubular degeneration was general. MacCallum described nodules, most numerous in the subcapsular zone of the testis. In these there were interstitial infiltration by wandering cells and later necrosis and mononuclear invasion of the included tubules. Such opaque, yellowish foci often showed hemorrhagic haloes. On healing small scars resulted. Mallory (1925) saw focal necroses surrounded by a moderate to well marked inflammatory reaction. Suppuration did not supervene.

Tyzzer inoculated rabbits intratesticularly with calf virus, producing an acute inflammatory reaction which he regarded as nonspecific. Henseval and Convent similarly produced testicular swelling and demonstrated vaccine virus in the testes. Paschen (p. 483) saw necrosis and cellular infiltration after intratesticular vaccination of rabbits.

Von Prowazek and Miyaji produced local necrosis at the site of inoculation into the testis. Noguchi saw multiple foci of interstitial polymorphonuclear infiltration appearing in twenty-four hours after intratesticular vaccination, followed by marked congestion, edema, enor-

mous interstitial infiltration by leukocytes and tubular hydropic degeneration increasing from the second to the fourth days and resulting in patches of tubular necrosis on the fourth day and breaking down of both tubules and leukocytes on the fifth day. Recession began on the sixth day; edema decreased, and foci of small round cells and fibrinous masses appeared, resolution proceeding to atrophy and fibrosis thereafter.

Levaditi and Nicolau first reported metastatic testicular "pustules" in the rabbit after intravenous vaccination. There were focal interstitial swelling, vacuolation and necrosis, going on to central caseous débris surrounded by a zone of many polymorphonuclears and few mononuclears. The included tubules were "altered," but less severely than the interstitial tissues.

Douglas, Smith and Price saw focal lesions of the testes, but gave no specific description of them. Bijl and Frenkel described swelling, degeneration and necrosis of the interstitial cells in the testis and degeneration of the tubules. Albugineal vaccinal lesions also occurred.

We saw following intratesticular inoculation severe hemorrhagic interstitial orchitis, with diffuse or focal, dense polymorphonuclear infiltration, or hemorrhagic necrosis and edema, more extensive in the interstitial tissue, but including surviving or necrotic tubules. Cutaneous and intravenous inoculations produced sharply defined focal coagulation necroses of the interstitial tissue. These were of varying size and contained fibrin, oxyphil débris, nuclear fragments and sometimes blood, including in the larger foci surviving or necrotic tubules and abutting marginally directly on apparently normal surviving tissue.

The variation of the focal lesions reported in the literature between infiltration, usually by mononuclear cells, and secondary pressure necrosis of the tubules, on one hand, and the frank focal necroses of the interstitial tissue preceding tubular degeneration and necrosis, on the other hand, appears to be simply a further manifestation of the variation in necrotizing power of the virus of variola and vaccinia.

OVARY, UTERUS AND TUBES

In hemorrhagic smallpox, Zuelzer saw hemorrhages in the female generative organs. Ponfick saw hemorrhages in the mucous surfaces of uterus, vagina and tubes, in the parametrium and in the substance of the ovaries. Roger noted an ovarian infarct. Ikeda noted uterine hemorrhages in purpuric cases.

Béraud and Robin described hyperemia and surface exudation on the ovaries. In pustular smallpox Perkins and Pay saw a hemorrhage in the stroma of the ovary. Councilman, Magrath and Brinckerhoff described ovarian focal infiltrations by large basophil cells and phago-

cytes in two cases. There were scattered single necrotic cells and some polymorphonuclear leukocytes.

Though the frequency of abortion during smallpox is a matter of common knowledge, decidual lesions appear never to have been studied either grossly or histologically. Consequently, experimental material bearing on this point assumes unusual interest.

Swelling, vacuolation and necrosis of the interstitial cells of the ovary in generalized vaccinia were reported by Levaditi and Nicolau. Polymorphonuclear invasion followed, but corpora lutea, graafian follicles and ova were not involved in their rabbits. Douglas, Smith and Price reported focal vaccinal lesions of the ovaries and uterus. Often the ovarian lesions could be differentiated from graafian follicles only by means of the microscope. The uterine lesions were small white spots or, often, protuberant umbilicated pocks on the peritoneal surface. Three pregnant animals showed necrotic débris replacing the fetuses, large, protuberant endometrial pocks and hemorrhagic peritoneal pocks. Histologically, the various lesions showed "typical necrosis with the usual peripheral cellular infiltration." Bijl and Frenkel saw diffuse and focal swelling and degeneration in the interstitial tissue of the ovary, leading to necrosis. Graafian follicles and their epithelium also took part in the necrosis. Few polymorphonuclear leukocytes were seen. Calcification appeared in later lesions. Ledingham and Barratt described hemorrhagic necroses without evidence of repair in the ovarian interstitial tissue. Polymorphonuclear leukocytes were lacking in early cases, but in some of the later ones they were present in vast numbers, in both ovarian and uterine focal necroses.

We described focal necroses of the endometrium in seventeen of thirty-six nonpregnant rabbits. The epithelial cells were oxyphil, coagulated and necrotic, their nuclei fragmented; the subjacent connective issue was filled with fibrin and fragmented cells and nuclei, often with hemorrhage, as well. Margination against surviving tissue was usually direct; in one late case there was central calcification with marginal proliferation of fibroblasts. Hemorrhagic necroses occurred also in the myometrium and parametrium. One pregnant uterus was studied. In this, the embryo was replaced by amorphous necrotic débris. The necrotic and surviving tissues showed a ragged irregular margin. There were masses of coagulated necrotic syncytium and Langhans cells, and in surviving decidual giant cells there were sometimes large vacuoles and small round cytoplasmic inclusion bodies about 1 micron in diameter. No walling off was seen, but some broken down pseudo-eosinophil leukocytes appeared.

In the ovaries, corpora lutea showed focal coagulation necroses closely resembling those in the suprarenal cortex, like them showing central débris, marginal, coarse vacuolation and late proliferation of

small lutein cells mingled with lymphocytes and small plasma cells. Focal coagulation necroses of the ovarian stroma were also reported.

We described a process in the follicular epithelium of the large graafian follicles, suggesting strongly that seen in other stratified epithelia. First there appeared vertical intercellular rifts and intracellular vacuoles, often perinuclear. The latter coalesced, setting free the nucleus, which soon became oxyphil with clumps of chromatin in it. The process was progressive, finally leaving many rounded, oxyphil nuclei and the necrotic ovum free within the basement membrane. During the process, vesicular spaces with vertical cellular trabeculae were sometimes formed.

Such endometrial lesions as those described by Douglas and his co-workers and by us, if they occur in smallpox, which seems probable, could well be the cause of the frequent abortions in this disease. It is hoped that this gap in the pathologic histology of variola may be filled.

MAMMARY GLANDS

Lesions of the mammary glands in smallpox have not been described, as far as I have been able to find.

In experimental vaccinia of rabbits, lesions have been seen by Levaditi and Nicolau, Douglas, Smith and Price and us. Douglas and his co-workers saw focal lesions in eleven animals, but published no histologic details. Levaditi and Nicolau saw multiple hemorrhagic foci showing degeneration and necrosis of the acinar cells and periacinar polymorphonuclear inflammation. We saw diffuse coagulation necrosis with discernible acinar outlines in one lactating gland, scattered necrotic acini in another, and in a nonlactating gland focal necroses involving acini and stroma, sharply marginated and without reaction.

THYROID AND PARATHYROID GLANDS

Roger and Roger and Garnier (1903) are the only authors who have reported on the thyroid gland in variola. Congestion, abundant colloid and minute hemorrhages in the parenchyma occurred in a case of confluent variola. Generally, the acini were smaller than normal, the colloid was decreased, and the epithelium was desquamated and proliferated to two or three layers, the last being absent in younger patients. Interacinar exudation of colloid was of regular occurrence as early as the second day (of the eruption?). No focal lesions were seen.

We described colloid depletion as occurring usually in experimental vaccinia, and we saw focal necroses in eight of forty-seven animals. These necrotic foci contained caseous débris and bordered on sometimes swollen but usually normal thyroid cells. One or several acini and the included interacinous stroma might be involved. Fibroblast proliferation appeared at the margins of the lesions at about the twelfth day.

We encountered a focal coagulation necrosis in the parathyroid gland in one instance. This contained coagulated oxyphil cells with karyolysis and karyorrhexis, and showed no marginal reaction.

The two reports cited appear to agree on the diffuse changes in the thyroid gland. Our report of focal necroses in the thyroid and parathyroid glands appears to be unique in the literature of variola and vaccinia.

GENERAL REFERENCES NOT ASSIGNABLE TO INDIVIDUAL ORGANS

McIntosh described lesions of the internal organs in postvaccinal encephalitis, which resembled tubercles, but showed more fibrosis. Giant cells were prominent and there was a peripheral zone of fibrosis and lymphocytes. From his failure to demonstrate tubercle bacilli and from the evidence of healing, McIntosh deduced that these lesions were not tubercles, and attributed them, apparently, to vaccine virus. His evidence against tuberculosis appears remarkably weak, as tubercles not infrequently heal, and tubercle bacilli are often difficult to demonstrate in sections.

McIntosh and Scarff saw multiple lesions in the skin, mucosae and viscera of rabbits inoculated with vaccine virus. The visceral lesions, without specific reference to any individual organ, were essentially in and around the smaller blood vessels. There was intimal proliferation and, in arterioles, adventitial proliferation and mononuclear, lymphocyte and eosinophil infiltration followed by thrombosis of the vessel and often necrosis. The necrotic foci were bordered by endothelial and giant cells and surrounded by fibroblasts, lymphocytes and plasma cells. The figures showed perivascular infiltration in the lungs. In my experience, perivascular infiltrations in the lungs of rodents generally and in the livers of rabbits are not uncommon, and though their significance is not clear, it does not appear probable that they are to be attributed specifically to the action of the vaccine virus. The granulomatous lesions described have been ascribed to coccidiosis, in the liver at least, by Ledingham and Barratt and have also been traced by me to cysts of *Taenia pisiformis* (unpublished data). It is regretted that these lesions were not referred by the authors to the organs in which they occurred.

CENTRAL NERVOUS SYSTEM

Fiedler, Roger and Southard saw no demonstrable lesions in the central nervous system in variola. Southard could find none mentioned in the literature. Perkins and Pay noted uniform congestion of the brain and cord, but did not report any histologic lesions. Eichhorst described foci of infiltration with mononuclear round cells and hemorrhages throughout the cord in smallpox. The infiltration was usually

perivascular and was either confined to, or transgressed, the lymphatic sheath. The nerve cells were swollen and stained poorly by Nissl's stain. Hyperemia and hemorrhages were seen in the pia.

McIntosh reported a case of smallpox in which the lesions were essentially the same as those seen in postvaccinal encephalitis. There was a perivascular small cell infiltration, slight in the adventitial space and diffuse in the surrounding parenchyma, where it was often accompanied by demyelination. The cellular infiltration consisted of large cells with clear oval nuclei and fewer lymphocytes. The pia was only slightly involved. Distribution was diffuse in the upper portions of the brain, diminishing downward, the medulla containing no lesions. The cord was not examined.

Since the encephalitis that has recently been so much reported as a complication of vaccination has been covered by Bijl in a comprehensive review, it would be futile to again go into what appears to be a more or less collateral subject other than briefly. Bijl summarizes the pathologic histology from the works of Luksch, Bastiaanse, Bijl and Terburgh, Turnbull and McIntosh, Van Hasselt, Bouman and Bok, Wiersma and lastly Perdrau as follows:

> The pia shows engorged, occasionally thrombosed vessels, occasional hemorrhages and infiltration by lymphocytes, plasma cells and cells of endothelial origin. The capillaries of the brain are congested. The sheaths of the blood vessels contain plasma cells, lymphocytes, polymorphonuclears and macrophages and are surrounded by a zone of cellular proliferation and demyelination. Focal nodules, chiefly of microglia, also foam cells and macroglia, are seen in various parts of the brain. Lesions are more pronounced and more numerous in the brain stem and basal ganglions, and fewer in the cortex.

Schürmann and Turnbull each reported essentially similar observations, and material from the case of Fulgham and Beykirch, furnished me by Dr. D. L. Harris, showed essentially the same picture. The case of Russell and Oddie showed no anatomic evidence of encephalitis, and its validity as a case of postvaccinal encephalitis therefore remains, at least, dubious.

In rabbits, lesions of the central nervous system have been produced almost exclusively by subdural or intracerebral introduction of vaccine virus. Levaditi, Harvier and Nicolau (1921-1922) described a dural pustule at the site of inoculation, in which were numerous polymorphonuclear leukocytes and here and there "veritable giant cells." There was diffuse perivascular infiltration of the pia by mononuclears. In the brain there were perivascular collars (small round cells are shown in the illustrations) and foci of polymorphonuclear infiltration. Lesions of nerve cells and neuronophagia were lacking. These last were first seen later in a cat (Levaditi and Nicolau). Condrea observed in the pia intense hyperemia, hemorrhages and diffuse infiltration by mono-

nuclear cells, plasma cells, rare polymorphonuclears and eosinophils, the last more intense in the gray and white substances of the brain (the text is not entirely clear; it is presumed perivascular infiltration was meant). Less frequent perivascular hemorrhages were seen in the brain. Condrea also described inclusion bodies in nerve cells and in fixed and desquamated ependyma cells, which he identified as Guarnieri bodies.

Luksch saw edema, hyperemia, polymorphonuclear infiltration of the pia and cortex, and round cell infiltration, especially about perforating vessels. Walthard (1926) obtained no meningeal or cerebral reaction on corneal vaccination; inoculating subdurally, he produced meningeal and superficial cortical perivascular cellular infiltration. Turnbull and McIntosh produced infiltration of the pia with lymphocytes, large lymphocytes, monocytes, "endothelial cells" and scattered polymorphonuclears and sleeves of round cells about perforating vessels in the brain. More intense reactions showed areas of serofibrinous exudation and necrosis in the pia and superficially about perforating vessels. McIntosh further noted definite areas of encephalitis in the brain and at times definite indications of perivascular softening. Ledingham and Barratt found no focal lesions attributable to vaccinia in the brains of three rabbits.

Levaditi, Nicolau and Sanchis-Bayarri inoculated apes and monkeys intracerebrally and saw hemorrhagic necrosis at the site of inoculation. Hemorrhage, polymorphonuclears, lymphocytes and granulo-adipose cells filled the lesion and extended out from it along the sheaths of the blood vessels. Degeneration of nerve cells was seen locally. Other parts of the brain were free from any lesion suggesting human postvaccinal encephalitis.

We described a serofibrinous, necrotizing leptomeningitis with extension inward a short distance along the sheaths of the blood vessels. This lesion was not produced in animals vaccinated cutaneously five or more days preceding subdural inoculation. We also saw foci of similar leptomeningitis three times among ninety-two animals inoculated by other routes. The round cell infiltrations of the pia and sheaths of blood vessels reported by other workers I found just as frequently in control material, and I attribute these to the spontaneous granulomatous meningo-encephalitis of rabbits.

It appears questionable to me whether postvaccinal encephalitis has been reproduced in rabbits, and on account of the great frequency of the spontaneous encephalitis, it will be difficult to obtain histologic proof of such reproduction. The fact that lesions similar to those of postvaccinal encephalitis have been found in two cases of smallpox does not in my opinion establish the vaccinal nature of the encephalitis, though it is not the present intention to challenge the view that postvaccinal encephalitis is due to the vaccine virus.

CONCLUSIONS

It would appear evident from the distribution of the lesions that the virus of variola and vaccinia is particulate. The primary effect appears to be cell injury, manifested by various forms of degeneration and necrosis. The inflammatory reaction appears to be mononuclear and proliferative, except when necrosis or secondary bacterial invasion has occurred. In this instance, the polymorphonuclear leukocyte participates to a greater or less degree. One of the effects of the lesser grades of cell injury is cell proliferation. The lesions of variola and of experimental and human vaccinia parallel each other to such a degree as to lead inevitably to the conclusion that the virus of the two diseases is one, showing, it is true, varying grades of virulence. The lesions of hemorrhagic smallpox have been reproduced in animals by some of the more virulent laboratory strains of vaccinia, as well as less severe forms. The present experimental evidence indicates that the bronchopneumonia of smallpox is a true focal manifestation of the disease.

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Notes and News

University News, Appointments, Promotions, Resignations, Deaths, etc.—J. G. Doull, of the school of hygiene and public health of the Johns Hopkins University, has been appointed professor of hygiene and public health in Western Reserve University, in the place of Roger G. Perkins, retired. Ramon F. Hanzal has been appointed instructor in pathologic chemistry in Western Reserve University.

At the University of Virginia, Oscar Swineford will have charge of the department of pathology for the coming year as acting professor.

At the University of Chicago, N. Paul Hudson has been appointed professor in the department of hygiene and bacteriology and Clay G. Huff assistant professor.

At Yale University, George Valley has been appointed assistant professor of bacteriology; H. M. Zimmerman, assistant professor of pathology, and D. M. Gay and C. G. Burn, instructors in pathology.

Frank Billings, formerly professor of medicine and dean of the faculty of Rush Medical College of the University of Chicago, has given $100,000 to establish four fellowships at the college, one of which is named in honor of E. R. LeCount, professor of pathology.

Withrow Morse, professor of physiologic chemistry and toxicology in Jefferson Medical College, Philadelphia, has retired from professional duties in order to devote himself to investigative work.

Samuel H. Gray has resigned as associate professor of pathology in the school of medicine of the University of Colorado to become pathologist to the Jewish Hospital, St. Louis.

Frederick E. Becker has been promoted to assistant professor of pathology in the school of medicine of the University of Colorado.

Benjamin White has been appointed assistant professor of preventive medicine and hygiene in Harvard Medical School.

George B. Magrath, medical examiner in Boston, has been appointed instructor in legal medicine at Harvard Medical School.

George Neil Stewart, professor of experimental medicine, Western Reserve University, has died at the age of 70.

Max Pinner, at present director of the laboratory, Maybury Sanatorium, Northville, Mich., has accepted an appointment in the Desert Sanatorium, Tucson, Ariz., and will begin his work there on October 1.

The board of scientific directors of the Rockefeller Institute announces the following promotions: associate member to member, Peter K. Olitsky; assistant to associate, Mortimer L. Anson, Robert B. Corey, René J. Dubos, Rebecca C. Lancefield, Dr. Currier McEwen, Alfred E. Mirsky, Albert L. Raymond, Julius Sendroy, Jr., and Richard E. Shope.

W. W. Brandes, instructor in pathology in the Northwestern University, Chicago, and pathologist to the Evanston Hospital, has accepted the appointment of assistant professor of pathology in Baylor University, Dallas, Texas.

Ralph Waldo Webster, clinical professor of medicine at Rush Medical College, University of Chicago, founder and director of the Chicago Laboratory and chemist to the coroner's office of Cook County (Chicago), died on July 2, 1930, at the age of 57. He graduated from Rush Medical College in 1898 and received

the degree of Ph.D. in chemistry from the University of Chicago. He was a member of the American Association of Pathologists and Bacteriologists and of the Society of American Bacteriologists. He served during the World War, wrote books on clinical diagnostic methods, edited the last edition of Peterson and Haines' Legal Medicine and Toxicology, and was widely known as an expert in toxicology.

Seventh International Congress of Medical History.—The seventh Congress will be held in September, 1930.

Archivio italiano di anatomica e histologica patologica.—This is a new bimonthly publication issued by professors of pathology A. Dionisi in Rome, A. Pepere in Milan and F. Vanzetti in Turin. The editors are N. Orlandi and R. Reitano, Ospedale Maggiore, Milan. The summaries of the articles are given in four languages: Italian, French, German and English. The contents are divided into original articles, reviews and brief reports. The subscription price per year is 150 lires outside Italy.

Research on Psittacosis.—The U. S. Public Health Service has established a laboratory for research on psittacosis at the quarantine station at Curtis Bay (Baltimore). Charles Armstrong will be in charge of the laboratory, and only persons who have had psittacosis are to engage in work there.

Obituary

KATSUSABURO YAMAGIWA, M.D.

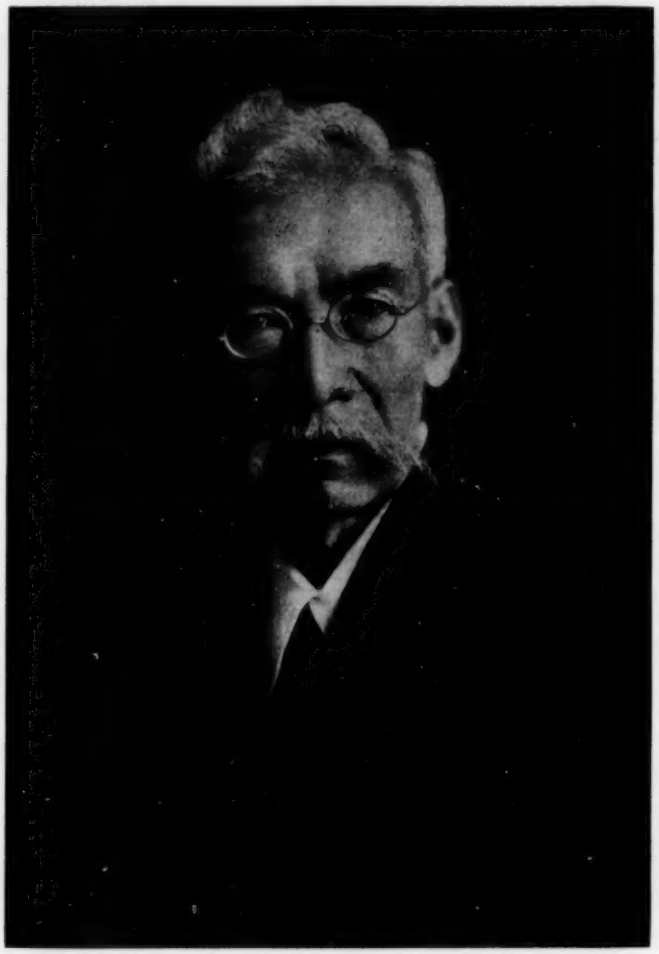
1863-1930

Katsusaburo Yamagiwa died on March 2, 1930, from pneumonia. He was born on Feb. 23, 1863, in Ueda, Nagamo Prefecture, Japan, and graduated in medicine from Tokyo Imperial University in 1888. In 1891, he became assistant professor in Tokyo Imperial University. He was sent to Germany for study, returning in 1894, when he was appointed professor of pathology, in which post he continued until he retired as emeritus in 1923.

Yamagiwa early became an active contributor to pathologic literature; his first papers dealt with inflammation and regeneration of tendons. In 1900, he published a paper on beriberi in which rice was suggested as a cause. In 1905, he published a monograph on cancer of the stomach and in 1911, a study of primary cancer of the liver. The work that made him famous was the demonstration in 1915, with Itchikawa, that cancer can be produced in the ear of the rabbit by the prolonged local application of coal tar. This epochal work was the outcome of an earnest and determined effort to settle by experiment whether chronic irritation and repeated minor traumas of various kinds may cause cancer. It is of interest to recall that Fibiger's demonstration in 1913 that cancer could be produced in the stomach of rats by feeding them with a certain parasite was hailed by Yamagiwa "as a glorious and stimulating achievement." Yamagiwa also produced cancer of the mamma in rabbits by the injection of tar. His experimental production of cancer has proved to be a most important advance, because his method offers a chance to search for the actual substance or substances at work and the precise way in which cancer is produced under such circumstances. Work of this kind is now being done and is yielding valuable results (see W. H. Woglom's review on Experimental Tar Cancer, ARCH. PATH. **2**: 533, 1926).

In 1906, Yamagiwa founded *Gann*, a journal devoted exclusively to the publication of results of research in the field of cancer, and now the official organ of the Japanese Society of Cancer Research. Yamagiwa became a member of the Imperial Japanese Academy in 1919, and in the same year he was awarded the Academy Prize in recognition of his experimental work on cancer. In 1929, he received the Sophie Prize from Germany.

Yamagiwa's name will live in the annals of pathology because he introduced a new and fruitful method in cancer research, based on sound experiments. Twenty years ago the possibility of inducing cancer at will seemed remote indeed. "The realization of that possibility, one



KATSUSABURO YAMAGIWA, M.D.

of the most significant victories of modern medicine, encourages the hope that even the problem of controlling cancer will be ultimately solved." In view of the achievements of Yamagiwa and others there is no room for the sterile, unwarranted pessimism of the notion that the problem cannot be solved.

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

THE EFFECT OF PARATHYROID EXTRACT AND CALCIUM UPON CALCIFICATION AND HEALING IN PULMONARY TUBERCULOSIS. BURGESS GORDON AND A. CANTAROW, Am. Rev. Tuberc. **20**:901, 1929.

A roentgenographic study of sixty tuberculous patients to whom parathyroid extract was given (10 units twice daily), from one to four months, showed no specific change in the course of the disease except as obtained through the relief of signs and symptoms, notably hemoptysis, pleurisy, cough and expectoration. There was no evidence of decalcification or increased calcium deposition in the lungs. Parathyroid extract (20 units every forty-eight hours) and calcium lactate (30 grains three times daily) were given to fourteen patients with pulmonary tuberculosis for a period of from one to six months. The results were the same as in the foregoing group and there was no change in calcification of the lung fields or bones of the hands and no visualization of the blood vessels. It appears that diseased or potentially diseased tissue is not influenced directly by hypercalcemia and that parathyroid hormone and calcium should not be administered with the expectation of inducing calcification. The influence of these agents on certain phenomena arising during the course of the disease may be considered of value in treatment.

H. J. CORPER.

THE EFFECT OF RACHITIC DIETS ON EXPERIMENTAL TUBERCULOSIS. AGNES H. GRANT, Am. Rev. Tuberc. **21**:102, 1930.

The addition of cod liver oil to diets which have been deficient in vitamin D decreases the resistance to tuberculosis that is already below normal. The addition of calcium to diet which had been deficient in both calcium and vitamin D does not seem to retard, in rats, the development of tuberculosis in the lungs.

H. J. CORPER.

THE EFFECT OF RACHITIC DIETS ON EXPERIMENTAL TUBERCULOSIS. AGNES H. GRANT, Am. Rev. Tuberc. **21**:115, 1930.

Resistance to tuberculosis can be decreased from a natural immunity to moderate susceptibility, without destroying the growth impulse, by prolonged disturbance in the optimal balance that should exist between the calcium, vitamin C and vitamin D of the diet. A prolonged excess of vitamin D in the diet, either with a deficiency of calcium or with a normal amount, hastens the spread of tuberculosis through the lungs. The substitution of vitamin C for vitamin D at the time of inoculation or the addition of vitamin C to a diet which is deficient in vitamin D tends to increase the amount of tuberculosis in the lung, rather than decrease it. The addition of vitamin C to a diet containing vitamin D tends to correct the diet, and to increase the resistance to tuberculosis. The degree to which diets corrected after inoculation can retard the spread of tuberculosis in white rats depends on the type of deficiencies and excesses in the diet before inoculation, and on how long the deficient diets have been given.

H. J. CORPER.

SICKLEMIA. JOSEPH LEVY, Ann. Int. Med. **3**:47, 1929.

In a routine study of fresh blood specimens of 213 negroes, the blood of twelve patients showed the sickling phenomenon. In only three of these cases was there

clinical evidence of the disease. Liver therapy produced marked improvement in these patients and apparently tends to inhibit the formation of sickle cells.

WALTER M. SIMPSON.

EXPERIMENTAL EDEMA IN DOGS IN RELATION TO HUMAN EDEMA OF RENAL ORIGIN. M. HERBERT BARKER and E. J. KIRK, Arch. Int. Med. **45**:319, 1930.

Edema in dogs, varying from a slight to a marked degree, can be produced by decreasing their serum protein. The amount of edema both in patients and in dogs seems more closely associated with the level of the serum albumin fraction than with the total protein. The basal metabolism of the dogs fell with the depletion of the blood serum. The blood volume in dogs was unchanged in the edematous period, but the cardiac output was greatly increased. Renal pathologic changes in dogs were produced by a low proteinemia, as shown by the appearance in the urine of albumin, granular casts, fat droplets and products of renal cell degeneration in the urine and by definite degeneration of the renal tubules, destruction of the glomeruli and scar tissue formation.

AUTHORS' SUMMARY.

THE ETIOLOGY OF EMPHYSEMA. L. M. LOEB, Arch. Int. Med. **45**:464, 1930.

Long continued high grade obstruction of the air passages of dogs was insufficient to produce a pathologic picture simulating vesicular emphysema in man. If obstruction is a factor, an additional factor or factors, as an associated infection of the finer respiratory passages is an essential concomitant. It is possible, but improbable that an expiratory obstruction much greater than inspiratory might be adequate.

AUTHOR'S SUMMARY.

THE PATHOGENESIS OF MULTIPLE SCLEROSIS. RICHARD M. BRICKNER, Arch. Neurol. & Psychiat. **23**:715, 1930.

While it is agreed that myelinolysis precedes gliosis in multiple sclerosis, it is not known what causes the destruction of the myelin. To solve this problem Brickner immersed pieces of fresh spinal cords from rats in oxalated plasma of patients suffering from multiple sclerosis. The dishes containing the plasma and cord were sealed with sterile petrolatum and placed at 37 C. for from twenty-four to forty-eight hours. Control plasma from healthy persons was used with the same method. The segments of the cord, after fixation in formaldehyde, were stained with hematoxylin and eosin, by the Marchi or Weigert-Pal methods. Brickner found changes in the cords treated by both pathologic and healthy plasma, but they were less marked in cords treated with plasma from healthy persons.

In general, the cord changes were mostly in the form of tumefaction of the myelin which took the stain well; the lacunae were more numerous and some sheaths showed fragmentation. The areas most suitable for study proved to be the anterior and the anterolateral columns. As the multiple sclerosis plasma invariably brought about changes in the white fibers, it is, according to Brickner, but fair to assume that it contains a myelinolytic factor. Such must be present also in normal blood, but in small quantities. The nature of the myelinolytic element is to be studied. In a limited number of cases of amyotrophic lateral sclerosis, post-encephalitic states and subacute combined cord degeneration no alterations were found which resembled those in multiple sclerosis.

GEORGE B. HASSIN.

LONG TIME FEEDING EXPERIMENTS WITH ACTIVATED ERGOSTEROL. C. A. BILLS and A. M. WIRICK, J. Biol. Chem. **86**:117, 1930.

The prolonged feeding of activated ergosterol to rats, in concentrations 100 times in excess of those necessary for the maintenance of a minimum antirachitic level, has no apparent effect on appearance, growth, reproduction or resistance to

respiratory infection. Toxic effects are manifest at overdosages of a thousandfold, and strongly evident at dosages in excess of forty thousand fold. The toxic action is augmented by calcium and diminished by phosphate. The administration of large overdoses of the vitamin to nursing rats does not result in the passage of more than a small amount into the milk. No significant quantity can be transmitted to rats in utero.

ARTHUR LOCKE.

THE SPECIFIC OXYGEN CAPACITY OF THE BLOOD COLORING MATTER IN PATHOLOGICAL CONDITIONS. H. ENGELKES, Quart. J. Med. **72**:507, 1929.

In determinations of the specific oxygen capacity of the blood of five normal persons, the author obtained values similar to those obtained by other investigators. In several cases of intraglobular sulphemoglobinemia, the specific oxygen capacity was found to be less than normal. It was, however, unchanged in secondary anemia. In a hemolytic process such as pernicious anemia or malaria, the specific oxygen capacity drops. Sulphemoglobinemia was also observed in animals, and the specific oxygen capacity was found to be somewhat lowered.

N. ENZER.

LACTIC ACID CONTENT OF MUSCLE AFTER DEATH CAUSED BY EXPERIMENTS WITH INSULIN. H. BAUER, Beitr. z. path. Anat. u. z. allg. Path. **83**:1, 1929.

If the normal rabbit is suddenly killed by a blow on the back of the neck, rigor of the musculature occurs in from four to eight hours. As has been long known, the chemical changes that occur in muscle and manifest themselves in rigor consist in a progressive decrease of the dextrose and glycogen of the muscle and a corresponding increase of the lactic acid. In previous work, it had been found that postmortem rigor of muscle occurs much more quickly in rabbits dying from an overdose of insulin than in normal animals. The usual postmortem increase of lactic acid did not occur in the muscles after death caused by insulin. The failure of the lactic acid to increase was associated with a low sugar and glycogen content of the muscle at the time of death. Since death due to insulin is preceded by muscular contractions like those caused by strychnine, the question that presented itself was whether the rapid onset of rigor, with a low lactic acid content, was not the result of the muscular contractions rather than of the insulin itself. Experiments designed to answer this question are presented in the present communication. Transection of the thoracic cord prevented the occurrence of contractions of the hind limbs following administration of insulin, but had no effect on the contractions of the fore limbs. Rigor of the fore limbs set in rapidly, as in control rabbits killed by insulin, whereas rigor was greatly delayed in the hind limbs. The chemical changes in the muscle of the hind limbs were similar to those of the muscle of a normal rabbit killed by a sudden blow, namely, a progressive decrease in glycogen and a corresponding increase in the acid-alkali index, as determined by the method of Wacker. The postmortem electric and mechanical irritability of the muscle of the hind limbs, after transection of the cord and administration of insulin, was found to be greatly increased as compared with that of the fore limbs. The increased irritability manifested itself by muscular twitchings that sometimes persisted for an hour after death. The heaping up in the muscle of carbohydrate split products, such as methylglyoxyl, is put forward as a possible explanation of the greater irritability of muscles in which convulsive contractions are prevented. This article is one of twenty that make up a number of the *Beiträge zur pathologischen Anatomie und zur allgemeinen Pathologie* issued as a "festschrift" in honor of the sixtieth birthday of Prof. Max Borst.

O. T. SCHULTZ.

EFFECT OF EXPERIMENTAL HYPERTHYROIDISM ON SEXUAL FUNCTION. G. DÖDERLEIN, Beitr. z. path. Anat. u. z. allg. Path. **83**:92, 1929.

For the experimental study of the interrelationships of the organs of the endocrine system, Döderlein considers the thyroid gland the most logical point of

attack. Its hormone has been isolated, and its specific effects can be determined. The measure of the end-result of a state of experimental hyperthyroidism was the sexual function. His report relates to experiments carried on for two and a half years. Young, sexually mature guinea-pigs were fed desiccated thyroid substance, the material being administered into the esophagus in daily doses of 0.05 to 0.1 Gm. The specific effect of the administered substance was determined and controlled by daily weighing of the experimental animals and biweekly determination of the basal metabolic rate.

Larger doses affect both males and females, the males apparently more than the females. Sexual desire and copulation are not influenced, but the male is rendered incapable of fecundating the female. Hyperthyroid females may become pregnant, but the pregnancy frequently ends in death and abortion of the young. When smaller doses are used, effects are noted in the first filial generation, again more marked in the male than in the female. The young of a hyperthyroid parent may exhibit evidences of hyperthyroidism at birth, but these rapidly disappear with the growth of the animal. An effect of longer duration manifests itself in the males when they become sexually mature; their sexual capacity is normal, but they usually fail to impregnate the female. Microscopic examination reveals no changes in the testis or ovary of animals in an experimental hyperthyroid state or of the offspring of such animals, although such animals are not functionally normal. The other endocrine organs, other than the suprarenal, reveal no changes. The suprarenal cortex is increased in thickness, the increase being chiefly of the zona fasciculata, which contains an increased amount of lipoid material.

The simplest explanation of the results obtained would be to suppose that thyroid hyperfunction directly affects sexual function. Since there is no morphologic support for such a view, the author believes that the effect is a more indirect one through the blood stream and an intermediate portion of the endocrine system, the latter, in the case of sexual function, probably being the suprarenal glands.

O. T. Schultz.

Hemolytic Splenomegaly with Paroxysmal Hemoglobinuria. Imre Barta and Dénes Görög, Virchows Arch. f. path. Anat. **273**:266, 1929.

The patient, a man, aged 34, knew nothing about jaundice in his family. The disease became manifest with anorexia, cramplike pains under the right costal arch and darkening of the urine. The patient was pale, not jaundiced, the spleen was slightly enlarged, the blood picture was normal and the resistance of red cells was from 0.45 to 0.34 per cent to sodium chloride. One year later the patient came to the hospital with abdominal pain, weakness, subicteric color, more enlarged spleen, urobilin in the urine, anemia, microcytosis and absence of reticulocytes. Resistance of red cells was from 0.42 to 0.30 per cent. The blood serum was reddish; the urine was the color of meat juice. There were no red cells in the sediment of the urine, but many granules of hemoglobin were present. Increasing anemia with microcytosis was noted, but there were no nucleated red cells. Splenectomy was performed, and during the two weeks following the blood picture improved rapidly; normoblasts and reticulocytes appeared. The patient died of thrombosis of the splenic, portal and mesenteric veins. The spleen (18 by 11 by 5 cm.) showed little histologic change; the blood was mostly in the pulp, the sinuses appeared compressed. Much blood was found in the loose tissue around the medium-sized arteries, the elastic layers of which were split. Iron pigment could be found only in the epithelium of the convoluted tubules of the kidney. The bone-marrow was aplastic.

In the discussion the authors stress the point that the resistance against sodium chloride is no true indicator of the real vitality of red cells. The disease could be called anhemopoietic hemolytic splenomegaly or aplastic hemolytic icterus. Autolysins and hemolysins were absent even during hemoglobinuria.

Alfred Plaut.

ENDOCRINE GLANDS IN LEAD POISONING. I. M. PEISSAKHOVITCH, Virchows Arch. f. path. Anat. **273**:276, 1929.

In dogs and cats poisoned by lead, the chromaffine substance in the suprarenal glands was found decreased. The total fat was increased, with changes in the mass relation between the different kinds of lipoid. There was some atrophy of the thyroid gland.

ALFRED PLAUT.

LIPOIDOSIS OF THE SKIN AND MUCOUS MEMBRANES. E. URBACH and C. WIETHE, Virchows Arch. f. path. Anat. **273**:285, 1929.

This detailed report deals with a new disease. The authors have made observations on nine patients belonging to four families. Shortly after birth, up to the second year of life, hoarseness was noted. Some of the patients suffered from recurrent stomatitis and tonsillitis during childhood. After vaccination, skin eruptions occurred which may have been eczema vaccinatum or variolois. All the patients had smallpox-like scars (the childhood symptoms otherwise are known from history only; the patients observed were adults). The skin lesions appeared later than the lesions of the mucous membranes in the mouth and larynx, which were responsible for the symptoms during childhood. In the adult, the skin of the face had a peculiar, sepia brown and greenish tint; there were many nodules the size of a pinpoint. Another lesion was represented by waxy, pale, yellow, miliary hard nodules, some the size of a lentil, which were located in the scalp chiefly. The hair was sparse. Some patients had similar lesions over the lips and the nose. In one the introitus vaginae was studded with yellow nodules. In the patients from one family one type prevailed; in the second family, another one. Yellow and brownish masses bulged from the mucosa of the lips, tongue and pharynx. The frenulum of the tongue was stiff and interfered with the forward movement of that organ. The sense of taste was impaired. The papillae of the tongue were atrophic. The epiglottis was much thickened, as were the vocal chords.

Histologically (many biopsies were taken), all superficial blood vessels of the skin and mucosa exhibited marked diffuse thickening of their walls, and there were enormous lipoid deposits. In sections from the older stages of the yellow nodules, large, homogeneous, partly round, more or less well outlined masses were seen, with few nuclei. In the small, wartlike lesions the deposits were more diffuse, and there was much overgrowth of blood vessels. It was similar with the mucosal lesions.

According to histochemical examinations, the deposits consisted of some lipoid which was physically combined with a protein. It was insoluble in alcohol, ether and chloroform, but was soluble in hot absolute alcohol and in boiling acetone. It became dark orange with sudan III.

The carbohydrate metabolism was disturbed in all nine patients. Either the blood sugar was high or the tolerance test gave a pathologic curve. Alimentary glycosuria was found three times. The differential diagnosis is discussed, notably from xanthomatosis and from hyperkeratotic lesions. Treatment may be necessary to prevent narrowing of the glottis by the deposits. Tracheotomy was performed in six instances. Cosmetically, electric removal of the lesions on the face is done. Radium treatments proved unsuccessful. Fat-free diet together with insulin treatment was of no avail. Treatment of the faulty sugar metabolism should be tried. In one patient considerable improvement followed the first pregnancy; the infant was normal.

ALFRED PLAUT.

LIPOMATOSIS OF THE PANCREAS AND ITS RELATION TO GENERAL OBESITY. J. BALÓ, Virchows Arch. f. path. Anat. **273**:320, 1929.

With Soxhlet's method of ether extraction, ten normal and ten lipomatous pancreases were analyzed for fat. By subtracting the figure for fat from that for the total dry substance, a parenchyma index was arrived at. This index was

much lower (5 to 12 Gm.) in the lipomatous than in the normal pancreas (11 to 20 Gm.). The atrophy of the glandular tissue is difficult or impossible to find by microscopic examination. The islands generally were well preserved, occasionally situated in fat tissue. It is unknown whether the atrophy is primary or secondary to the lipomatosis. Probably the islands as well as the exocrine part of the pancreas have to do with obesity.

ALFRED PLAUT.

Pathologic Anatomy

LYMPHATIC LEUKEMIA WITHOUT LEUKOCYTOSIS. C. M. HYLAND, Am. J. Dis. Child. **39**:59, 1930.

Three cases of lymphatic leukemia without leukocytosis are reported. Two of these cases came to autopsy and presented the pathologic picture of leukemia. The other patient died at home and no permission for postmortem examination was obtained. In all cases the white blood count was low (8,600 being the highest), but in all there was a high percentage of lymphocytes. No immature cells were found save for a single myelocyte noted in one of the cases in which autopsy was done. All cases were characterized by glandular enlargement, severe anemia and fever.

J. N. PATTERSON.

CIRRHOSIS OF THE LIVER IN CHILDHOOD. T. LEONARD SUTTON, Am. J. Dis. Child. **39**:141, 1930.

The nature and occurrence of cirrhosis in childhood are discussed. The thirteenth American case of nonalcoholic primary atrophic cirrhosis of the liver in a child is reported. A warning is given concerning the easy confusion of primary cirrhosis with Banti's disease in relation to the question of splenectomy. The onset of the disease with a disturbance like catarrhal jaundice, and the occurrence of large spider angiomas of the skin in association with cirrhosis are again emphasized.

AUTHOR'S SUMMARY.

ALTERATIONS IN THE VOLUME OF THE NORMAL SPLEEN AND THEIR SIGNIFICANCE. JOSEPH BARCROFT, Am. J. M. Sc. **179**:1, 1930.

The volume of the normal spleen of the dog was studied by two methods: (1) estimating of the size of the organ by means of x-ray photographs, taken in horizontal and vertical planes, following a preliminary operation in which small metal clips were placed along the edge of the spleen; (2) observing the size, following an operation in which the spleen was exteriorized without injury to the vascular and nervous attachments. Pregnancy produced prolonged contraction of the spleen. A similar contraction is seen after intestinal operations. The spleen buffers mechanically the vascular system against sudden emergencies, but the explanation of the shrinkage in intestinal operations in pregnancy and in heat remains in the dark. It is thought that a large increase in the vascular bed of the generative organs accounts for the shrinkage during pregnancy and heat.

JOHN PHAIR.

THE AGRANULOCYTIC BLOOD PICTURE IN CONDITIONS OTHER THAN ANGINA. GEORGE BLUMER, Am. J. M. Sc. **179**:11, 1930.

There are cases of local and general sepsis with an agranulocytic blood picture, aside from the well-recognized group of agranulocytic anginas. It is not yet clear whether the sepsis or the loss of power of the bone-marrow to form granulocytes is the primary lesion. Such cases cannot be differentiated clinically from acute aleukemic lymphatic leukemia with terminal infectious processes. In some instances it may be difficult to differentiate them from aplastic anemia with terminal infection.

AUTHOR'S SUMMARY.

THE INVOLVEMENT OF THE CORONARY ARTERIES IN RHEUMATIC FEVER. SOLOMON R. SLATER, Am. J. M. Sc. **179**:22, 1930.

A case of thrombosis of the coronary artery due to rheumatic disease with characteristic electrocardiographic observations is reported. The symptomatology and pathogenesis of rheumatic coronary arteritis are discussed.

AUTHOR'S SUMMARY.

EOSINOPHILIA IN LIVER DIET. E. MEULENGRACHT AND SIGRID HOLM, Am. J. M. Sc. **179**:199, 1930.

Eosinophilia in liver treatment of pernicious anemia has appeared in a marked and persistent form when the treatment is carried out with raw liver (calf) in large doses. As a rule, the eosinophilia has appeared rather suddenly after about four weeks of treatment, and it has reached high degrees—20, 40, even 74 per cent. In seems to persist as long as the administration of raw liver is kept up. On treatment with fried liver (calf) or liver extract, the phenomenon has usually been absent; and when present in single instances, it was in a faint and transitory form. Persons studied as control who were suffering from various other diseases have responded to the treatment in the same manner as have patients with pernicious anemia, as they constantly showed eosinophilia on ingestion of raw liver but not after intake of fried liver or liver extract. This eosinophilia is to be considered a by-product in the treatment for pernicious anemia with raw liver that has nothing to do with the curative effect of the treatment. As far as directly observable, the eosinophilia represents a harmless phenomenon.

AUTHORS' SUMMARY.

EOSINOPHILIA WITH SPLENOMEGALY. FRANCIS F. HARRISON, Am. J. M. Sc. **179**:208, 1930.

A case is reported with marked eosinophilia and an enlarged spleen. No parasites were found. Autopsy revealed a hyperplastic bone-marrow filled with eosinophils and in the spleen and lymph nodes very many eosinophils and occasional eosinophilic myelocytes. Similar cases are reported from the literature. The belief is expressed that these cases constitute a clinical entity.

AUTHOR'S SUMMARY.

INTESTINAL POLYPOSIS WITH AN INSTANCE OF MULTIPLE FIBROMATOUS POLYPS. J. GOTTESMAN AND DAVID PERLA, Am. J. M. Sc. **179**:370, 1930.

Two cases of multiple polyposis of the intestine are reported. The first is an instance of multiple fibromas of the small and large intestine associated with chronic tuberculous enteritis. A relation between the chronic irritation and the development of the polyps is suggested. The second instance is one of multiple adenomatous polyps of the intestine complicated by intussusception and malignant degeneration. These two instances again emphasize the etiologic rôle of chronic irritation in the formation of new growths.

AUTHORS' SUMMARY.

THE CLINICAL AND ANATOMIC DESCRIPTION OF A NAEGELE PELVIS. J. WHITRIDGE WILLIAMS, Am. J. Obst. & Gynec. **18**:504, 1929.

Williams describes a pelvic deformity in a negress who had six uneventful and spontaneous deliveries. The outstanding feature of the pelvic menstruation was an asymmetry in which the right oblique diameter was 2 cm. shorter than the left, and the distance from the spine of the last lumbar vertebra was 2.25 cm. greater to the right than to the left anterior superior spines. In the seventh

delivery the progress was slow and version extraction was made. Manual removal of the placenta was likewise necessary. Some hours later a traumatic rupture of the uterus necessitated a supravaginal hysterectomy. Death occurred on the twenty-fifth day from a tuberculous pneumonia. The pelvis and the last two lumbar vertebrae were removed, and examined carefully. It was a typical Naegele pelvis or obliquely ovate pelvis, in which the left sacro-iliac joint had been obliterated, a considerable part of the left ala of the sacrum disappeared, and what remained of it had become firmly synostosed with the left innominate bone. The diameter of the right posterior superior spine to the left anterior superior spine was 15.75 as compared with 19.75 cm. of the corresponding opposite diameter. This indicated that in the right oblique diameter delivery was almost impossible and in the other diameter a small fetus could be delivered. There was no atrophy of the left inominate bone. Roentgenograms of the left sacro-iliac joint showed that the bony fibers extended continuously and pursued a regular course which did not favor an ankylosis secondary to an inflammatory process. There was nothing in the history to indicate a previous inflammatory process. This is offered as a case which does not support the contentions of Breus and Kolisko that a previous inflammatory process is the basis of this type of pelvic deformity.

A. J. KOBAK.

THE PACCHIONIAN SYSTEM. N. W. WINKELMAN AND TEMPLE FAY, Arch. Neurol. & Psychiat. **23**:44, 1930.

Winkelman and Temple Fay studied the condition of the pacchionian granulations in a series of more than 200 cases, from a great variety of clinical and pathologic conditions. In fourteen cases they found aplasia of these bodies, that is, their absence; even their immature forms, arachnoid villi, were scarce. Such a type—evidently a developmental anomaly—occurred in eight cases of idiopathic epilepsy and several cases of hydrocephalus of unknown etiology.

In the second group (twenty-eight cases), hypoplasia was the prominent feature. Here the pacchionian bodies are present but not fully developed and show no evidence of functional activity. They are usually represented by groups of mesothelial cells within the meshes of the dura. In the third group, hyperplastic conditions, the pacchionian granulations are enormously dilated and their contents (myxomatous material) are stained homogeneously with the acid dyes. With some stains a fibrillary network can be demonstrated containing vacuoles filled with granular material. This form was observed in acute uremia, acute alcoholism and other "hydropic" conditions. The fourth group comprised "fibrosis" (forty-two cases). Here the pacchionian granulations are fibrosed, shrunk and atrophied; the fibrils are very dense. This type occurs in conditions in which the soft membranes of the brain are fibrosed (in dementia paralytica, arteriosclerotic conditions and chronic alcoholism) and clinically in cases associated with frequent convulsions. In group five (fifty-three cases) are included infiltrative conditions. Here the pacchionian granulations contain the same abnormal elements that are found in the subarachnoid space (inflammatory cells as seen in acute forms of meningitis, tuberculosis and syphilis; they also contain blood or blood pigment). The changed pacchionian bodies, whatever the type, cause insufficient escape of the cerebrospinal fluid. This accumulates around the bodies and causes their atrophy from pressure. Certain cases of hydration and a tendency toward convulsive seizures are also considered by Winkelman and Fay as the result of the pathologic state of the pacchionian structures. These, they think, not only possess a definite physiologic function but also present a definite pathologic condition. The significance and effect of the latter, however, they admit must be determined by subsequent studies.

GEORGE B. HASSIN.

THE NATURE OF VON RECKLINGHAUSEN'S DISEASE AND THE TUMORS ASSOCIATED WITH IT. WILDER PENFIELD AND ARTHUR W. YOUNG, Arch. Neurol. & Psychiat. **23**:320, 1930.

The clinical symptoms in Penfield and Young's patient, a girl, aged 21, were difficulty in walking, deafness, impaired vision, headache and dizziness. The earliest complaint was headaches at the age of 14, followed by disturbances of gait, dizziness, deafness, first in the left and later in the right ear, blurred vision and speech troubles. A diagnosis of tumor of the brain was made. The patient's condition allowed only a suboccipital craniotomy after which total blindness set in and the deafness became worse. The patient died of respiratory paralysis.

At necropsy, multiple subcutaneous nodules were found over the surface of the body, in the mesentery of the ileum, the lesser curvature of the wall of the stomach, without involving its mucosa; in the sympathetic ganglions (one of which displaced the right suprarenal gland forward); in the left auditory nerve (size 5.5 by 3.5 cm.) which distorted the pons, medulla and cerebellum, and a smaller tumor (the size of a split pea and well encapsulated) in the right auditory and facial nerves. Small tumors were attached to the left oculomotor, right trigeminal nerves, and pea-sized tumors were seen along the glossopharyngeal, the vagus, the spinal accessory and the hypoglossal nerves; the first, second and fourth cranial nerves escaped. In the spinal cord, the tumors were numerous in all the roots of the cauda equina; they were scarce on the anterior roots; scattered throughout the dura, in both dorsal and ventral portions of the brain and the spinal cord, were many small nodules (4 by 4 mm.). In the brain (white matter, optic thalamus) many soft areas were present. In short, the meninges and the central and peripheral nervous systems were involved. Histologically, the tumors of the spinal nerve roots and the peripheral nerves presented a mixture of connective tissue, nerve fibers and cells of Schwann; often also nerve fibers were present; the nuclei of the tumor were elongated and arranged in a palisade form; they stained poorly for reticulin with Hortega and Perdrau's methods; with van Gieson's they assumed a yellowish-brown tone; the fibroglia fibers stained blue with Mallory's phosphotungstic acid stain. The authors consider the widely accepted designation of such tumors as neurinoma "unfortunate" and use instead Mallory's definition "fibroblastoma." The numerous connective tissue fibers found in such tumors (designated by Antoni as type B) are just the result of a reaction. The tumors of the cranial nerves were typical neurofibromas with superimposed areas of fibroblastomas which were also found in the tumors of the roots and peripheral nerves. The tumors of the meninges (mainly dura) were made up of fibroblasts which differed from such of the perineural type and "possessed the characteristics peculiar to the cells of the meninges." The neoplastic growth was associated with a nonneoplastic reaction of the same cells in the warty eruptions of the dura. In the spinal cord one section showed an ependymoma (in the center); near by (near the ventral surface of the cord) was an astrocytoma; a definite neuroglia reaction was present at another level of the cord and in the same section, overlying the cord, was an area of typical meningeal fibroblastoma in the pia-arachnoid. In the cerebrum, one area showed a conglomeration of blood vessels which justified the diagnosis of hemangioma; another area in the brain contained an astrocytoma and something similar was present also in the cerebellum. As a reaction to the astrocytes, areas of gliosis were present. In all the tissues (connective tissue sheaths of the nerves, the meninges and the central nervous system) in which multiple tumors were present in this case there were definite signs of hyperplastic reaction of the cells peculiar to those tissues. The authors assume that in von Recklinghausen's disease various tissues are under the influence of some irritant which results in their hyperplasia. The neoplastic growth of the tissue cells is merely a superimposed phenomenon being thus the result of an irritation rather than that of some embryologic factors.

GEORGE B. HASSIN.

CORTICAL ANOMALIES, VENTRICULAR HETEROTOPIAS AND OCCLUSION OF THE AQUEDUCT OF SYLVIUS. JAMES W. KERNOHAN, Arch. Neurol. & Psychiat. **23**:460, 1930.

Heterotopias of the brain tissues are usually multiple. In Kernohan's case they were associated with congenital occlusion of the aqueduct of Sylvius, a rare occurrence. The patient, a girl, aged 3 years, had hydrocephalus and epilepsy. She was normal at birth, but at the age of 4 months was undernourished, and when she was 1 year old epileptic convulsions developed. The child was an idiot; she never talked or walked and had disturbed sensations, but could hear a little. The head was large and was not influenced by lumbar punctures. Death occurred during status epilepticus. There were dilated lateral and third ventricles, thin walls and numerous reddish-brown nodules (from 1 mm. to 1 cm. in diameter) scattered over the lateral and superior walls of the lateral ventricles; the aqueduct of Sylvius was partly closed; the tissue around it was gray and gelatinous. The fourth ventricle was normal. Histologic studies revealed absence of the ependyma from the walls of the lateral and third ventricles and a widened subependymal glia layer which became in some areas continuous with the heterotopic nodules. The latter contained many irregularly arranged ganglion cells, which varied in size; axis cylinders were absent; glia cells were excessive but no glial fibrils were present. Basal ganglions, cerebellum, pons and medulla oblongata contained no nodules. The lamination of the cortex was, with some exceptions, fairly well retained. In some areas the cortex had a mottled appearance because of loss of cells; many ganglion cells appeared immature; some as Betz cells were greatly diminished in numbers; often they were collected in groups and showed signs of degeneration; the optic thalamus was practically devoid of ganglion cells. Signs of inflammation were absent throughout. The cause of the occlusion of the aqueduct was most likely congenital.

GEORGE B. HASSIN.

HYPEROSTOSIS AND TUMOR INFILTRATION OF BASE OF SKULL ASSOCIATED WITH OVERLYING MENINGEAL FIBROBLASTOMA. N. W. WINKELMAN, Arch. Neurol. & Psychiat. **23**:494, 1930.

The tumor occupied the left anterior part of the brain, extending to the lateral surface of the temporal, motor and posterior parts of the undersurface of the temporal lobe and the posterior part of the orbital surface of the frontal lobe; it was associated with marked thickening of the left orbital roof which was four or five times the size of the opposite side and was closely adherent to the dura. The tumor was a fibroblastoma with a collection of few tumor cells in two small narrow spaces of the thickened orbital bone. While thickening of the bones of the skull may be associated with meningeal tumors, their invasion by the latter has not been described.

GEORGE B. HASSIN.

FUNCTIONAL CIRCULATORY DISTURBANCES AND ORGANIC OBSTRUCTION OF THE CEREBRAL BLOOD VESSELS. FRIEDRICH HILLER and ROY R. GRINKER, Arch. Neurol. & Psychiat. **23**:634, 1930.

Hiller and Grinker assume with others that actual changes in the brain may be caused by functional vascular disturbances, such as stasis, prestasis and ischemia, just as they may be caused by organic changes in the blood vessels. As an example of the former, they describe the histologic changes in a case of pertussis eclampsia. A child, aged 3 years, while recovering from whooping cough, had several convulsions within six weeks and in one day before admission to the hospital had as many as seven. Clinically, the child showed constant twitchings of the muscles of the anterior part of the left thigh, loss of power of the left arm, absence of abdominal reflexes and "normal Babinski reflex." Ten days before death a paresis developed on the right. Necropsy showed bronchopneumonia,

areas of softenings in the cortex at the level of the rostrum of the corpus callosum and some foci irregularly scattered throughout the frontoparietal lobes. The blood vessels were hyperemic, but not thrombosed and the meninges appeared normal. Brain changes were in the right hemisphere (mostly in the third and fourth lamina) in the form of ganglion cell degeneration, proliferation of astrocytes and microglia cells which were filled with fat (stage of astrocytic proliferation). The next stage was termed incomplete softening—the degeneration of the ganglion cell progressed further and the microglia cells developed into gitter cells, while the astrocytes showed regressive changes. The third stage was that of complete softening—the field consisted of fat laden gitter cells which were gathered also around the blood vessels. In areas of severe softening, the latter showed proliferation of endothelial cells and perivascular infiltrations with lymphocytes and plasma cells, but no endarteritis or proliferation of blood vessels was present. Quite affected was Ammon's horn, especially Sommer's sector, and the gray matter of the basal ganglions. The white matter showed mucinoid degeneration but no areas of softening.

The second case was an example of changes in the brain caused by thrombosis or possibly embolism of the middle left cerebral artery in a woman who died from an ulcerative endocarditis. The main change in the brain was an extensive softening of the left superior and middle temporal gyri, extending from the prerolandic area back to the gyrus, including the insula. The parenchyma was edematous and the cortex in the region affected was necrotic, but the white matter was preserved. Microglia showed no reactive phenomena which were present in the bordering areas. In general, the destruction was much more advanced.

GEORGE B. HASSIN.

ON UTERINE CASTS. J. PRESTON MAXWELL, J. Obst. & Gynec. Brit. Emp. **36**: 544, 1929.

Casts of the uterus are classified by the author as: (a) those from early abortion, (b) those from ectopic pregnancy, (c) those associated with menstruation, and (d) those of doubtful origin. Examples are given of each type and illustrated. Those from intra-uterine pregnancies are diagnosed by the demonstration of villi, but those in the other groups are difficult to classify since the presence of decidual-like cells is not a positive indication of pregnancy.

A. J. KOBAK.

ECTOPIC ENDOMETRIUM IN A MACACCUS RHESUS. A. D. FRASER, J. Obst. & Gynec. Brit. Emp. **36**:590, 1929.

This case is offered as the first nonexperimental evidence of ectopic endometrial growth in a lower animal. The animal in question was killed "for reasons which had no concern with its state of health," and no clinical data are included in the report. The umbilical region was swollen by a firm encapsulated tumor the size of a walnut. In the mesentery of the ilium there were twenty-three firm nodules varying in size, the largest about 1 inch in diameter, and a brownish pedunculated pea-sized growth was seen attached to the right sacro-uterine fold. Endometrial tissue was found in all these growths. They varied in appearance; some appeared to be in the resting stage, some in the premenstrual, and others were cystic and lined with flattened epithelium. There was no endometrial tissue found in connection with the ovaries, and the tubes were patent.

A. J. KOBAK.

SALPINGITIS ISTHMICA NODOSA AND TUBAL ADENOMYOSIS. OSCAR FRANKL, Arch. f. Gynäk. **135**:556, 1929.

The nodular thickening of the isthmic portion of the tube originates, in the majority of cases, on inflammatory basis. Deep growths of the tubal epithelium with tubal formation with simultaneous muscle hypertrophy are results of an inflammation with or without abscess formation. The old term of "salpingitis

isthmica nodosa" is therefore correct. In rare cases there is another genesis for nodular thickening of the isthmic and interstitial portions of the tube. Either it consists in an adenomyosis from the uterus, or a heteroplasia of the tubal epithelium in the tubal musculature. In such cases as in uterine adenomyosis there is no inflammatory basis. Therefore in these rare cases the designation of tubal adenomyosis is adequate. A true case of adenomyosis may be associated with a secondary inflammatory process, making it difficult to determine its origin. Cases of this sort are not suitable for studying the cause of the tubal swelling.

A. J. KOBAK.

CONGENITAL STENOSIS OF POSTERIOR URETHRA. M. BECK, Beitr. z. path. Anat. u. z. allg. Path. **83**:13, 1929.

Beck reports two cases of congenital infracollicular stenosis of the urethra. In one case in a boy aged 3½, the stenosis was situated at the junction of the prostatic and membranous urethra. The corpus spongiosum of the penis, with the urethra, lay dorsal to the corpora cavernosa, which were not separated from each other by the usual median longitudinal septum. The meatus of the glans penis was dorsal, the coronary sulcus ventral. The bladder was small and contracted. The ureters were greatly dilated and convoluted. The wall of the lower segment of the left ureter contained a rudimentary accessory ureter. The renal pelves were dilated. In the second case, in a new-born male infant, the stenosis was situated in the membranous portion of the urethra. There were no anomalies of the penis except phimosis. The left testis was retained in the inguinal canal, the right in the abdomen. The bladder was distended and reached to the level of the umbilicus. The ureters were tortuous and moderately dilated. An accessory ureter situated in the anterior and mesial wall of the main ureter of each side opened into the bladder laterally to the normal ureteral opening. The accessory ureters ended blindly above. The renal pelves were dilated. The kidneys were small and polycystic. The pelvis of the left kidney was situated anterior to the lower pole of the kidney.

O. T. SCHULTZ.

INTRAPERITONEAL HEMORRHAGE ASSOCIATED WITH MYOMA OF THE UTERUS. O. BRAKEMANN, Beitr. z. path. Anat. u. z. allg. Path. **83**:63, 1929.

In the three cases presented by Brakemann, intraperitoneal hemorrhage occurred suddenly at the time of menstruation. In the first case, a clinical diagnosis of myoma of the uterus had been made some months before the sudden onset of hemorrhage. The tumor had previously caused no symptoms. At operation, a large amount of free blood was found in the peritoneal cavity. The surface of a large, degenerated fibroid of the uterus was covered by a network of greatly dilated veins. Hemorrhage had occurred from erosion of one of the varicosed veins. Increased filling of the enlarged veins at the time of menstruation and rubbing against the bony pelvis were considered factors in the erosion. In the second case, the hemorrhage resulted in death before surgical intervention could be undertaken. At necropsy, there was found a large fibromyoma of the uterus. This was adherent to the sigmoid in a region in which there were two ulcer-like depressions of the mucosa. The mucosa itself was, however, intact. The wall of the sigmoid in this region and the adhesions contained misplaced endometrial tissue, from which the fatal intraperitoneal hemorrhage had occurred. The latter was held to have been due to erosion of a blood vessel by the cytogenous stroma of the misplaced endometrial tissue rather than to menstruation of the latter. In the third case, laparotomy revealed intraperitoneal hemorrhage and a ruptured tubal pregnancy. The uterus contained many fibroid nodules, and the wall of the uterus was the seat of diffuse endometriosis. Although the hemorrhage in this case was due to the most frequent cause of intra-abdominal bleeding, namely, rupture of a tubal pregnancy, the myomatous condition is held to have been a contributing factor, in that it prevented uterine implantation of the ovum.

O. T. SCHULTZ.

CLASSIFICATION OF CHRONIC ENLARGEMENTS OF THE SPLEEN. W. HUECK, Beitr. z. path. Anat. u. z. allg. Path. **83**:152, 1929.

Looking on the spleen as a purely mesenchymal organ which has deviated less from the embryonic mesenchymal state than has any other organ, Hueck presents an analysis and classification of chronic enlargements of the spleen. He leaves out of consideration enlargements due to specific inflammations or to tumor formation. The remaining enlargements of longer duration, as opposed to the acute swellings of infectious diseases, he divides into three groups: (1) those due to swelling, (2) those due to infiltration, deposition or storage and (3) those due to growth or hyperplasia. Swelling may be due to edema, of the occurrence of which in pure form in the spleen little is known, or to hyperemia. The later may be arterial or venous. Arterial hyperemia begins in the subcapsular or perifollicular zones, but may lead to filling of all the blood spaces of the spleen, in which case it is not to be distinguished from venous hyperemia. Transmission of the pulse wave causes rupture and hemorrhage, which may lead to iron and calcium incrustation. Arterial hyperemia may regress without causing permanent changes, or it may lead to hyperplastic changes. Venous hyperemia begins in the peritrabecular sinuses. It may regress without causing permanent alterations. If of sufficient duration, it causes changes the nature of which depends on the site of the hindrance to venous outflow. If the obstruction is central or beyond the liver, most of the tissue is in a state of venous engorgement with sluggish circulation, the spleen being large, firm and dark red. Peristence of such engorgement leads to cyanotic atrophy and sclerosis of the spleen; the organ become small, tough and pale. Portal stasis also causes venous engorgement, but this leads to hyperplasia, especially of the reticulum about the sinuses. Hemorrhage and iron and calcium incrustation are frequent. Enlargement due to infiltration, deposition or storage may involve either the cells or the ground substance or both. The greater degrees of such enlargement are usually associated with hyperplasia, as in Gaucher's disease. The reticulum may undergo softening, because of edematous infiltration, or hardening, due to amyloid or hyaline deposition. Growth or hyperplasia may be cellular or reticular in origin. Most of the splenic enlargements detected clinically belong to this group. The cellular hyperplasia may involve the so-called germinal centers of the follicles, a process noted chiefly in the young. Or it may involve the perifollicular zone, when it may be either myelopoietic or lymphopoietic. Hyperplasia of the reticulum leads to diffuse growth of the spleen. The reticulum that undergoes hyperplasia may be that of the follicles, to which process the author applies the term lymphadenosis. It may be the pulp reticulum, which bears no direct relation to the follicles or the sinuses; this process is seen in the chronic splenic enlargements of chronic sepsis, anemia or hemolytic icterus. It may be the reticulum about the sinuses, such being the case in venous hyperemia due to portal stasis. If the growth processes are associated with marked variations in the degree of vascular engorgement, there results a peculiar condition that the author terms fibro-adenia. By this, the author understands a progressive stiffening and condensation of the ground substance, which becomes difficult of differentiation from the reticulum. The author's use of this term seems to differ somewhat from that of Eppinger.

O. T. SCHULTZ.

OSTEITIS OF THE JAW OF DENTAL ORIGIN. H. SIEGMUND, Beitr. z. path. Anat. u. z. allg. Path. **83**:289, 1929.

Siegmund presents a general discussion of changes in the alveolar processes of the jaws of dental origin. Students of general pathology have paid little attention to such alterations. The older view that the peridental membrane acts as a periosteum to the root of the tooth is no longer tenable. It, together with the tooth, and the alveolar process form a unit structure or tooth organ. Inflammatory changes that reach the apex of the tooth root through the root canal quickly involve the membrane and the surrounding bone. Acute purulent inflammation, which is

rare, leads to destruction of the spongy bone of the alveolar process in a manner that does not differ from a similar involvement of any other spongy bone. Chronic inflammatory reactions may follow an acute stage, but more frequently develop gradually as the result of less severe infection by way of the root canal. Such chronic inflammations do not remain limited to the peridental membrane, but cause changes in the bone for a considerable distance about the root of the tooth. The bone becomes rarefied by the resorptive action of the inflammatory tissue that is formed. The so-called granuloma which is often seen attached to the root of an extracted infected tooth consists only of the inflammatory tissue formed at the apex of the tooth. The bone is involved for some distance about the site of the granuloma. Chronic osteitis about a root need not be the result of infection. It may be an aseptic process, brought about by the chemical used in root canal fillings. In accepting this possibility, Siegmund accepts also Stricker's theory of the rôle of circulatory disturbance as a primary factor in setting up inflammation. If, after extraction of the tooth, epithelium becomes embedded in the healing tissues of the socket, a cyst may be formed. Complete healing cannot occur if a cyst has been formed. If no cyst is formed, healing may occur by the new formation of bone. If the involved root is situated near the surface of the bone, as may be the case with some of the molar teeth, the chronic inflammatory process may spread to the cortical bone and periosteum of the mandible or to the antrum of the maxilla. Siegmund's discussion is based in part on the microscopic study of human material, and in part on the study of lesions produced experimentally in dogs.

O. T. SCHULTZ.

PERIARTERITIS NODOSA DIAGNOSED DURING LIFE. W. STEPP, Deutsche med. Wchnschr. **56**:437, 1930.

A man, aged 31, had symptoms of marked polyneuritis after a drinking spree and complained of violent pain in the abdomen resembling gallstone colic. He had a moderate septic fever and a slight leukocytosis. The blood pressure was increased and the urine contained casts, albumin and a few leukocytes. The neurologic symptoms were the only physical changes. The occurrence of polyneuritis with abdominal colic, nephritis and a septic fever suggested the diagnosis of periarteritis nodosa. Postmortem examination demonstrated a perforated gastric ulcer and generalized peritonitis. There were infarcts and abscesses of the kidneys. The microscopic examination disclosed a periarteritis nodosa.

PAUL J. BRESLICH.

THROMBI AND TUMORS OF THE HEART. FRANZ WINDHOLZ, Virchows Arch. f. path. Anat. **273**:331, 1929.

The presence of myxomatous tissue in a pedunculated mass attached to the endocardium of antrium cordis does not prove the neoplastic character of the lesion. The author gives a description of different portions and the different layers of such a large mass. He interprets it as an organized thrombus. The thrombus was surrounded by endocardium. The thin pedicle contained no blood vessels. In three of nine parietal thrombi of the left auricle, homogeneous material was found in spots which, however, was not mucin. In a cherry-sized mass which also was attached to the edge of the fossa ovalis, the myxomatous change could be seen with the naked eye, but the thrombotic origin of the whole formation could be proved nevertheless. On the other hand, the endocardial metastases of a bronchial carcinoma and a sarcoma of femur contained myxomatous structures without any thrombosis being present. The formative power of the ever-moving heart blood acts in the same way on tumors and thrombi. This throws some light on the much involved discussion about neoplastic or nonneoplastic origin of intracardial thrombi or myxoma.

ALFRED PLAUT.

Pathologic Chemistry and Physics

THE DIFFUSIBILITY OF CALCIUM IN BRONCHIAL ASTHMA AND ALLIED DISORDERS, AND IN PULMONARY TUBERCULOSIS. A. CANTAROW, Am. J. M. Sc. **179**:497, 1930.

The present study appears to indicate that in bronchial asthma and allied disorders there is a definite and constant disturbance of calcium balance in the form of an increase in the ratio of diffusible to nondiffusible calcium. It is conceivable that this observation is related in some way to the increased capillary and cellular permeability which is believed to exist in these conditions. In chronic pulmonary tuberculosis there is considerable variation in the diffusibility calcium. It seems that an increased diffusibility ratio is associated with an exudative type of lesion with a high degree of clinical activity, while a decreased diffusibility ratio is associated with a productive process, relatively benign clinically. Whether or not these findings bear any relation to the problem of allergy in tuberculosis cannot be stated definitely but the implication is obvious.

AUTHOR'S SUMMARY.

THE BLOOD-CALCIUM CONTENT IN PULMONARY TUBERCULOSIS. VERA B. DOLGOPOL, Am. Rev. Tuberc. **20**:931, 1929.

In moderately advanced pulmonary tuberculosis the blood-calcium content is increased. In the advanced stage only the far advanced C (National Tuberculosis Association classification) shows an average calcium content below the average normal and a decreased incidence of cases with a high calcium content. The other far advanced groups (A and B) do not show any evidence of decalcification. The decalcification in the far advanced C group is the result of malnutrition. In moderately advanced pulmonary tuberculosis the highest calcium content is observed in the age group from 21 to 40 years, and the lowest above the age of 40. In far advanced pulmonary tuberculosis the patients over 40 years of age show the highest calcium content. A drop of the calcium content to below 9.2 mg. per hundred cubic centimeters of serum is a sign of imminent death.

H. J. CORPER.

THE ACID-BASE COMPOSITION OF GASTRIC JUICE DURING THE SECRETORY CYCLE. THEODORE L. BLISS, Ann. Int. Med. **3**:838, 1930.

Bliss determined the acid-base composition of the gastric juice during the secretory cycle of three human beings and one dog with a Pavlov pouch. The concentration of chloride was increased after stimulation except in the achlorhydric state, but in amounts that were less than the increase in the concentration of free hydrochloric acid. During the secretory cycle the concentration of base varied inversely to the concentration of acid. Sodium was found to be the most significant of the individual bases, both in amount and in its relationship to the variation in the total base during the secretory cycle. The concentration of the determined ions was found to be less in the stomach than in the blood serum, with the exception of potassium. The concentration of potassium was from three to five times greater in the gastric juice than in the blood serum.

WALTER M. SIMPSON.

THE SIGNIFICANCE OF CHANGES OF VISCOSITY IN PATHOLOGICAL SERUM. E. H. FISHBERG, J. Biol. Chem. **85**:465, 1930.

An attempt has been made to analyze the factors contributing toward an abnormal viscosity of the blood serum in cyanosis, nephrosis, uremia, pernicious anemia and obstructive jaundice.

ARTHUR LOCKE.

FORMATION OF A COLORLESS FORM OF HEMOGLOBIN AFTER SPLENECTOMY. G. B. RAY and L. A. ISAAC, J. Biol. Chem. **85**:549, 1930.

Spectrophotometric examinations have been made of the blood of dogs, following splenectomy. The results have been interpreted to indicate the presence, in such blood, of a colorless derivative of hemoglobin which may become transformed into hemoglobin on reduction, and into methemoglobin on oxidation.

ARTHUR LOCKE.

CYSTINURIA. E. BRAND, M. M. HARRIS AND S. BILOON, J. Biol. Chem. **86**:315, 1930.

The compound which passes through the kidney in cystinuria is not necessarily free cystine. A more complex precursor, similar in structure to glutathione, may be concerned. Evidence is presented that the cystine content of the urine, as estimated by the Sullivan method, may be only minimal at the moment of excretion, and may later increase at a rate suggestive of the completion of an intermediate decomposition process.

ARTHUR LOCKE.

URORUBIN, A NEW PIGMENT OF THE URINE. M. WEISS, Klin. Wchnschr. **9**: 248, 1930.

Under the name urorubin, a new urinary pigment is described, which arises from a chromogen by exposure to sunlight. The pigment, which is demonstrable spectroscopically, has some relation to diabetes, to cardiac and vascular diseases and to certain infectious diseases, especially tuberculosis and convalescence following catarrhal jaundice.

AUTHOR'S SUMMARY.

Microbiology and Parasitology

A SURVEY TO DETERMINE THE PREVALENCE OF TUBERCULOUS INFECTION IN SCHOOL CHILDREN. H. W. HETHERINGTON, F. MAURICE MCPHEDRAN, H. R. M. LANDIS and EUGENE L. OPIE, Am. Rev. Tuberc. **20**:413 and 421, 1929.

Tuberculin tests of school children of Philadelphia show that 37.7 per cent are infected with tuberculosis at the age of 5 years and 90.2 per cent at the age of 18 years. These figures indicate that there has been no significant diminution of the incidence of tuberculous infection during childhood to correspond with the diminution of mortality from tuberculosis in recent years. The intracutaneous tuberculin test is the only accurate method of determining the incidence of tuberculous infection in apparently healthy children. American born children of Italian parentage have shown a low incidence of tuberculous infection. In Jewish children attending school, being more frequent in highschool children than in other children. Pulmonary tuberculosis recognized by roentgenologic examination in association with symptoms and physical signs is found in 0.5 per cent of children attending school, being more frequent in highschool children that in children of elementary schools. Latent apical tuberculosis recognizable in roentgenologic films is often the precursor of the adult type of pulmonary tuberculosis. It is found in 1 per cent of adolescent children (of highschool age) and is more frequent in girls than in boys. Latent tuberculous infiltration of the lung of childhood type was found in more than 1 per cent of the children. These lesions may be the precursor of grave disease. Latent tuberculous foci in lungs and tracheobronchial lymph nodes are found in more than 10 per cent of school children. It may be the precursor of pulmonary tuberculosis. It varies from massive caseous lesions of serious import to firmly calcified foci, which are evidently healed. Its significance is determined by the size of the lesion, the activity of the tuberculin reaction, continued exposure to open tuberculosis, associated changes in the lung substance and the age of the child. Pulmonary tuber-

culosis recognized by roentgenologic examination together with symptoms and physical signs was found more than twice as often in adolescent girls as in boys of the same age. It is approximately four times as frequent in colored as in white children of highschool age. The evidence suggests that tuberculous infection may spread within schools but under the existing system of medical school inspection this seldom occurs.

H. J. CORPER.

EXPERIMENTAL PNEUMONOKONIOSIS (REACTIVATION OF HEALING PRIMARY TUBERCLE IN THE LUNG BY THE INHALATION OF QUARTZ, GRANITE AND CARBORUNDUM DUSTS). LEROY U. GARDNER, Am. Rev. Tuberc. **20**:833, 1929.

Guinea-pigs were primarily infected by the inhalation of tubercle bacilli of low virulence. In normal animals such infection produces isolated subpleural pulmonary tubercles which caseate, then retrogress and finally heal by resolution. As a part of the picture of primary infection, the tracheobronchial lymph nodes are also involved, and the lesions in this location undergo a similar series of changes. At intervals of from fifty-four to 206 days after such infection animals were removed to dust chambers where they were exposed to the inhalation of quartz, carborundum and granite dust until they died or were killed. The inhalation of these dusts stimulated a renewed multiplication of bacilli in the healing tubercles, and this was followed by widespread chronic ulcerative tuberculosis. At least two months' exposure to the dust is necessary to affect the primary foci of infection. Marble and soft coal exhibited no stimulating effect. The reaction appears to be a specific result of the inhalation of certain types of dust and factors like overcrowding, lack of proper ventilation and light, endemic pneumonia and nonspecific inflammations have not influenced this type of tuberculous infection. In partial explanation of the results it was shown that a renewed multiplication of bacilli took place only in those tubercles containing ample amounts of dust, in which the dust particles had been carried into the nodules by phagocytes. Relatively few quartz particles were ingested by any one phagocyte, and the activity of these cells was not affected; perhaps it was even accelerated. So many carborundum and granite particles were taken up by the majority of the cells that their power of locomotion was lost and very little dust was carried into the tubercles. Various theories are discussed and it is believed that the data can be applied to pneumonokoniosis in human beings. It is believed that in a certain proportion of cases in man in which dust of the proper type is inhaled, this may stimulate preexisting quiescent foci of infection.

H. J. CORPER.

THE SUSCEPTIBILITY OF THE HAMSTER (CHINESE FIELD MOUSE) TO THE TUBERCLE BACILLUS. GEORGE Y. C. LU, Am. Rev. Tuberc. **20**:938, 1929.

Hamsters are susceptible to minute amounts of tubercle bacilli. As high as 85 per cent were successfully infected with approximately ten to fifteen bacilli. About 50 per cent showed tuberculous lesions ten weeks after inoculation with probably not more than one or two living bacilli. The first evidence of tuberculous infection after the inoculation of a few tubercle bacilli appeared about four weeks after inoculation. Exposure of hamsters to the roentgen rays before the inoculation of tubercle bacilli had no effect on shortening the time elapsing before tuberculous lesions appeared.

H. J. CORPER.

THE INFLUENZA EPIDEMIC OF 1928. EUGENE F. TRAUT and RUSSELL D. HERROLD, Arch. Int. Med. **45**:412, 1930.

The flora in the sputum of patients acutely ill with influenza were identical in containing two predominating types of bacteria: green-producing streptococci

and gram-negative diplococci. The streptococci of these patients were pathogenic for animals. These streptococci produced a toxin. Skin tests with this toxin suggested a means of determining susceptible persons. Vaccines from these streptococci seemed to have the power of immunizing against the influenza infection. The green-producing streptococci for the most part reacted similarly in fermentation tests and bile-solubility tests. These streptococci showed relationship in cross-agglutination experiments.

AUTHORS' SUMMARY.

THE RELATIONSHIP OF YELLOW FEVER OF THE WESTERN HEMISPHERE TO THAT OF AFRICA AND TO LEPTOSPIRAL JAUNDICE. W. A. SAWYER, S. F. KITCHEN, MARTIN FROBISHER, JR., AND WRAY LLOYD, J. Exper. Med. **51**:493, 1930.

The yellow fever now occurring in South America, the present yellow fever of Africa and the historic yellow fever of Panama and other American countries are the same disease. This conclusion is based on cross-immunity tests in monkeys with strains of yellow fever virus from Africa and Brazil and on tests of serums from twenty-five persons, who had recovered from yellow fever in various places and at various times, for the power to protect monkeys against African or Brazilian virus strains. Cases of leptospiral jaundice (Weil's disease) were present among those diagnosed as yellow fever in the recent epidemic in Rio de Janeiro. This is shown by the isolation of cultures of *Leptospirae* from the blood of two patients by H. R. Muller and E. B. Tilden of the Rockefeller Institute, and by the demonstration by us of protective power against *Leptospirae* and absence of protective power against yellow fever virus in the serums from two persons after recovery. The isolation of *Leptospirae* by Noguchi and other investigators from the blood of occasional patients in past epidemics of yellow fever in a number of American countries indicates that leptospiral jaundice was present then as well and was diagnosed clinically as yellow fever. The absence of protective power against *Leptospirae* shown by the Brazilian serums which protected against yellow fever virus and the absence of protective power against yellow fever virus in the serums that protected against *Leptospirae* point to the probability that American yellow fever is not the combined effect of *Leptospirae* and yellow fever virus. The position of *L. icteroides*, isolated by Noguchi during epidemics of yellow fever, now appears to be not that of a secondary invading micro-organism in cases of virus yellow fever, but that of the incitant of a form of infectious jaundice, sometimes fatal, often coincident in its appearance with typical yellow fever and apparently indistinguishable from it clinically. This leptospiral disease has not hitherto been separated from true yellow fever. Noguchi's discoveries become, therefore, of the greatest significance in respect to the epidemiology and causation of yellow fever and of infectious jaundice, previously confused one with the other. In all outbreaks of supposed yellow fever hereafter the existence of the two kinds of jaundice, one due to yellow fever virus and the other to *Leptospirae* will have to be taken into account. Only the former probably is spread by mosquitoes and requires antimosquito measures for its control. The only difference observed between the American and African strains of yellow fever virus was a pronounced difference in virulence for monkeys. The virulence of the two African strains studied was high, while that of the one American strain was highly variable and usually low.

AUTHORS' SUMMARY.

THE SKIN AS A PORTAL OF ENTRY IN BR. MELITENSIS INFECTIONS. ALBERT V. HARDY, MARGARET G. HUDSON and CARL F. JORDAN, J. Infect. Dis. **45**:271, 1929.

It seems clear that there is more than one possible portal of entry in *Br. melitensis* infections. Our object was to determine the relative importance of

the different sites of entrance. That undulant fever may be acquired by ingesting organisms is universally accepted. That the infection might gain entrance through the skin has also been recognized, but this has heretofore been given too little consideration. Our experiments show that the normal skin of guinea-pigs is more vulnerable as a portal of entry than is the digestive tract, and the epidemiologic evidence indicates that the same is true of humans. Since the organisms gain entrance without causing any local lesions, the probable portal can be determined only by considering carefully the types of exposure, the dosage and the resistance to invasion at the different portals. On a consideration of these points it seems probable that *Br. melitensis* frequently gains entrance through the skin to produce undulant fever in man. Furthermore, judging from experimental data, ingestion is not a satisfactory explanation for the natural and ready transmission of contagious abortion among animals, and we believe that, for animal infection also, more consideration should be given to the skin as a portal of entry for *Br. melitensis.*

AUTHORS' SUMMARY.

THE PATHOGENICITY OF THE SPECIES OF THE GENUS BRUCELLA FOR MONKEYS. I. FOREST HUDDLESON and E. T. HALLMAN, J. Infect. Dis. **45**:293, 1929.

Our data indicate quite clearly that *Br. abortus* (Bang) is pathogenic for the monkey, in which it produces a disease resembling undulant fever. Infection, however, is not readily produced and in many cases does not occur at all. Monkeys are very susceptible to infection from a small dose of the *suis (porcine)* species of *Brucella* regardless of its source. In fact the data indicate that this species is more virulent for the monkey than is the *Br. melitensis* species.

AUTHORS' SUMMARY.

THE RESISTANCE OF SCARLET FEVER STREPTOCOCCI TO THE ACTION OF BACTERIOPHAGE. JOHN E. WALKER, J. Infect. Dis. **45**:304, 1929.

Streptococci from erysipelas are in general susceptible to lysis by the streptococcus bacteriophage described by Shwartzman. Scarlet fever streptococci so far tested are resistant. It also appears that epidemic sore throat strains are susceptible to lysis when freshly isolated. Streptococci may lose their susceptibility to lysis on cultivation on artificial mediums. Other strains may retain their susceptibility even after ten years' cultivation. All nonhemolytic streptococci tested were resistant to the bacteriophage.

AUTHOR'S SUMMARY.

THE GROWTH OF PASTEURELLA AVICIDA IN THE FOWL. L. D. BUSHNELL and V. D. FOLTZ, J. Infect. Dis. **45**:308, 1929.

The results obtained indicate that there is a marked difference in individual cells of the same bacterial culture. Some cells are capable of surviving in the body of the bird while others are not. In artificial mediums practically all the cells present seem to be able to survive and grow. There is a difference in the vegetative function and aggressive function of bacterial cells. This difference is probably the basis of virulence in these organisms. *P. avicida* appears to have an organ virulence for blood and is able to grow irrespective of the manner in which introduction is made. The organisms possess so little toxicity that they do not call forth any marked response on the part of the host. However, the exudation into the lungs may be due to serotoxins or some product due to the interaction of the bacteria and serum or tissue cells which does not appear in artificial culture.

AUTHORS' SUMMARY.

A STUDY OF CERTAIN HEMOLYTIC STREPTOCOCCI OF THE BETA TYPE IN CERTIFIED MILK. EDITH HAYNES, J. Infect. Dis. **45**:316, 1929.

The majority of hemolytic streptococci of beta type in certified milk which either do not hemolyze at all in fluid mediums, or do so only slightly, are members of

group 7 according to the classification of Brown, Frost and Shaw. This group closely resembles *Str. mastitidis* (group 2) in cultural and biologic characteristics. Some of the strains found in certified milk which do not hemolyze in the test tube are members of group 9. This group is very similar to group 4 which does hemolyze in fluid mediums. Groups 7 and 9 differ in their fermentation of salicin and in their appearance on blood agar plates. Many of the strains of group 9 produce double or triple zones of hemolysis around the colonies. Strains belonging to group 8 are found infrequently. Strains of groups 7 and 9 usually do not hemolyze in fluid mediums, but this test is not constantly negative. The age of the inoculum and the age of the culture tested affect the hemolytic titer in the standard test only slightly, but an inherent quality in the culture probably is more often the source of variation. This test is, however, considered sufficiently reliable to use as a basis of classification. The slight tendency for the weakly hemolytic strains to show hemolysis in the tube indicates a close relationship between them and the strongly hemolytic strains. None of our cultures which had been kept on artificial mediums for some months proved pathogenic for mice. A narrow capsule may be present on young cultures of group 7. This is not so distinct or obvious as the capsule of *Str. epidemicus* (Davis) and does not persist so long. All the strains studied hydrolyze sodium hippurate. Growth of these strains in litmus milk is very similar to that of other streptococci which ferment lactose, and this test is of no differential value. A temperature of 58 C. for twenty minutes is sufficient to kill these strains in a lightly inoculated medium. They probably would not survive pasteurization unless present in milk in large numbers. Agglutination tests show a close serological relationship between groups 2 and 7. Groups 3 and 4 do not seem to be so closely related to group 7. Group 7, to which most of our strains belong, seems from both a cultural and serologic standpoint to be a very homogeneous group. This group is distinguished from group 2 only by a weak hemolytic titer.

AUTHOR'S SUMMARY.

PATHOGENICITY OF TWO STRAINS OF HERPETIC VIRUS FOR MICE. H. B. ANDERVONT, J. Infect. Dis. **45**:366, 1929.

Two well known strains of herpetic virus of different pathogenicity for the rabbit, namely, the JB and Levaditi strains, were used for studying the activity of the virus in mice. The conclusions attending these studies are as follows: Mice react to both strains when inoculated intracranially; in fact, mouse-brain constitutes a delicate test object for each. Seventy-five mouse-brain passages of the JB virus and 21 mouse-brain passages of the Levaditi virus failed to produce any marked change in their pathogenicity for the rabbit. Dilution tests in mice show that the JB virus is more virulent than the Levaditi virus. Mice are susceptible to pad, corneal, intracutaneous, intraperitoneal and intravenous injection with JB virus. Mice are highly susceptible to traumatized skin inoculation with either virus. No marked difference in pathogenicity between the two strains is detected with this test. The virus tends to become more generalized in mice after skin inoculation than after brain inoculation. Intraperitoneal injection of active virus produces immune mice. Mice immune to the JB strain are also immune to the Levaditi strain and vice versa. Serum of herpes-immune rabbits neutralizes the mouse-passage virus in vitro and confers passive immunity on mice. New-born of actively immunized mice are immune to skin inoculations with either strain for approximately two weeks.

AUTHOR'S SUMMARY.

PATHOGENIC SPORE-BEARING ANAEROBES IN THE CARCASSES OF SHEEP. I. E. NEWSOM, FLOYD CROSS and HERTA S. DOBBINS, J. Infect. Dis. **45**:386, 1929.

Pathogenic spore-bearing anaerobes may be isolated from the spleens of a considerable proportion of sheep dead of a variety of diseases. In the case of *Cl. oedematis* the longer the animal has been dead the greater is the likelihood

of its presence in the spleen. *Cl. oedematis* is not the cause of the disease described by the authors as overeating. Caution should be exercised in attributing etiologic significance to the presence of *Cl. oedematis* in the tissues of sheep.

AUTHORS' SUMMARY.

UNUSUAL TYPES OF NONLACTOSE-FERMENTING GRAM-NEGATIVE BACILLI FROM ACUTE DIARRHEA IN INFANTS. LEROY D. FOTHERGILL, J. Infect. Dis. **45**:393, 1929.

A group of organisms called, although incorrectly, "atypical paratyphoid" bacilli have been found in the stools of a high percentage of patients suffering from "summer diarrhea." This group of organisms, although called here "atypical paratyphoid" bacilli, do not belong in the paratyphoid genus nor to any of the known genera of gram-negative intestinal bacilli. This group of organisms has in common the following characteristics: they are nonmotile; they do not liquefy gelatin; they do not ferment lactose or else ferment it with a latent reaction, and all sugars fermented are fermented with acid and gas production. Within this group, agglutination shows that they are not an homologous group like the typhoid bacillus. Of these organisms, a sucrose-fermenting subgroup occurred in about one third of the carefully studied cases, and the serum from a few patients with this organism in the stools showed agglutination, but in one case agglutination was negative. With other types of organisms in the main group, the patients' serums in the very few cases studied showed no agglutination. The study of this group of organisms as related to infantile diarrhea is far from complete and much remains to be done before one would be justified in drawing any definite conclusions concerning the etiology.

AUTHOR'S SUMMARY.

AN OUTBREAK OF FOOD POISONING CAUSED BY SALMONELLA ENTERITIDIS. RIGNEY D'AUNOY, J. Infect. Dis. **45**:404, 1929.

An outbreak of food poisoning following the ingestion of cream puffs infected with *Salmonella enteritidis*, which affected ninety persons, is reported. All patients recovered. Agglutinins for a recovered strain of *S. enteritidis* and for old laboratory cultures were noted in two cases, in one of which an acute endocardial involvement developed during the course of illness. None of the food handlers showed agglutinins for this or closely related micro-organisms, nor could any significant forms be isolated from their feces. *S. enteritidis* was isolated from rodent excreta found in the bakery, as well as from the intestinal contents of mice trapped therein. Intraperitoneal injection of the recovered organism in mice and guinea-pigs caused death, but feeding live and killed cultures to a limited number of rabbits and guinea-pigs produced no observable symptoms.

AUTHOR'S SUMMARY.

THE LEUKOCYTOSIS IN SCARLET FEVER IN RELATIONSHIP TO SERUM TREATMENT AND COMPLICATIONS. MARGARET E. WYLIE, J. Infect. Dis. **45**:408, 1929.

The leukocyte count is a less reliable index of the severity of scarlet fever than is the general clinical picture and can seldom be used as an index of the severity or of the progress of a case of scarlet fever with respect to the probable onset of complications. In uncomplicated and complicated cases of scarlet fever a pronounced fall in the white cell count, between the first and third day, is a constant finding. There is no evidence to indicate that the administration of antitoxin in cases of scarlet fever has any effect on the leukocyte count from admission to the seventh day of illness. In cases of scarlet fever a polymorphonuclear leukocytosis is the rule, but the excess of polymorphonuclear cells is slight, and their proportion

does not undergo much variation throughout the course of the disease nor does it differ characteristically in the complicated and uncomplicated cases. The behavior of these cells does not distinguish the simple from the complicated cases. From the first day onward the small lymphocytes undergo a steady and constant increase. The large lymphocytes increase from first to third day but decrease thereafter until by the seventh day their original level is virtually regained. This constant curve is independent of the occurrence or nonoccurrence of complications and of the giving or withholding of serum.

AUTHOR'S SUMMARY.

THE HERPES-ENCEPHALITIS PROBLEM. FREDERICK P. GAY and MARGARET HOLDEN, J. Infect. Dis. **45**:415, 1929.

From a critical survey of the literature on experimental herpes and on epidemic encephalitis it is pointed out that the only well maintained hypothesis as to the causation of the latter disease is the one sponsored primarily by Levaditi. Epidemic encephalitis may well be caused by a neurotropic strain of the virus of herpes simplex, acting under a combination of favoring conditions. Evidence in favor of this hypothesis would seem to be accumulating and apparent disproof of this explanation has become less persuasive. At all events the continued experimental study of the nature and mode of action of the herpes virus offers the best present method of approach to the encephalitis problem, be it only in nature of analogy. In addition, information obtained from the study of herpes enlightens the complex problem of the nature of virus diseases in general. Our studies are based largely on the examination of a strong neurotropic herpes virus (Le Fevre) without demonstrable dermotropic properties, compared with a less neurotropic virus ("Frank" by Flexner) which readily produces a characteristic herpetic eruption. The Le Fevre virus is adsorbed and neutralized by carmine powder and partially adsorbed without neutralization by charcoal. It is readily precipitated in large part with the globulins of carbon dioxide whence it can be extracted integrally by 5 per cent sodium chloride solution. Desiccation and conservation of the virus were possible but only at a low temperature. Direct freezing of the brain with or without carbon dioxide gas yields a preparation that can be ground and dried to a homogeneous powder for an as yet undetermined period retains its original properties of disease production. The Le Fevre virus when inoculated in or on the skin disappears within a few hours (± 24) and without producing any well defined lesion. Rapid passage through the skin at shorter intervals apparently does not render the virus any more dermotropic. Repeated injections of the virus in various parts of the body frequently produce a very irritative form of dermatitis often at a distance from the point of inoculation. This lesion varies distinctly from the characteristic herpetic lesion produced by the Frank virus. Rabbits withstand relatively large doses of the Le Fevre virus in the pleural cavity, when administered in a single dose. When an easily tolerated dose is divided over a period of days or weeks it is always fatal. This greater susceptibility is not, however, due to a process of specific sensitization but apparently to structural changes that may be induced by indifferent substances in the granulating pleura. Immunization by the actively neurotropic Le Fevre virus is very difficult and dangerous by intraperitoneal, subcutaneous and intravenous routes. Intradermal inoculation though relatively harmless does not readily lead to protection. The ideal method of producing active immunity both in rabbits and guinea-pigs lies in provoking an herpetic eruption by scarification or intradermal inoculation by means of the Frank virus. This is quite harmless and leads rapidly on recovery to a strong generalized immunity not only against the Frank but also the Le Fevre and H. F. strains. Active immunity is characterized by the presence of virucidal properties in the serum. No alexin-fixing or precipitating antibodies were found even in hyperimmunized rabbits. The virucidal antibody is easily demonstrable by allowing the serum to act on the herpes-producing virus (Frank) and injecting the mixture intradermally

in rabbits or guinea-pigs. Continued inoculation of a horse with the Le Fevre virus produced no virus-neutralizing property in the serum of this animal.

AUTHORS' SUMMARY.

THE PRODUCTION OF STAPHYLOCOCCAL TOXIN. F. M. BURNET, J. Path. & Bact. **33**:1, 1930.

Under the experimental conditions used, strains of *Staphylococcus aureus* incubated in broth for from three to five days do not produce appreciable quantities of hemolysin unless a considerable proportion of albus variants appear or the cultures are incubated in an atmosphere containing added carbon dioxide. The albus variants give rise to moderately stable cultures that produce large amounts of hemolysin in broth or on agar without the necessity for more than traces of carbon dioxide. In broth, the albus type produces hemolysin only while the medium is on the acid side of neutrality. Large yields of toxin can be obtained by extracting the agar beneath a twenty to twenty-four hour growth of a staphylococcus grown under suitable conditions. The carbon dioxide requirements for the two types to produce toxin are the same for agar as for broth cultures. Equivalent amounts of albus and aureus types from the same strain differ in their buffering capacity, the albus strain being more effective. The results are discussed from the standpoint that the function of carbon dioxide in bacterial physiology depends on its power to pass freely into the organisms and alter the intracellular p_H independently of that of the environment.

AUTHOR'S SUMMARY.

THE PATHOGENESIS OF, AND PROPAGATION OF THE VIRUS IN, EXPERIMENTAL POLIOMYELITIS. R. W. FAIRBROTHER AND E. WESTON HURST, J. Path. & Bact. **33**:17, 1930.

After intranasal and intracerebral inoculation in monkeys, poliomyelitis spreads histologically from above downward, the various levels of the cord becoming involved more or less simultaneously. Owing to the greater individual susceptibility of the anterior horn cells, and particularly those of the lumbar region, paralysis usually appears, and later becomes complete, first in the legs; the clinical signs are thus no guide to the path of entry or manner of spread and development of the disease. Spread of the infection to the brain stem and cord occurs by way of the axis cylinders and this appears to be the route usually taken to other parts of the central nervous system; meningeal spread is, however, possible and probably always plays some part in the local dissemination of the infection around the site of inoculation. Meningitis is therefore not the primary lesion of the disease, which begins as a primary degeneration of nerve cells accompanied by inflammation in the interstitial tissues. Virus is present in greatest amount in those regions in which nerve cell degeneration is particularly severe, that is to say, in the spinal cord and brain stem; where nerve cell degeneration is slight, as in the cerebral cortex, in spite of the existence of numerous foci of inflammation, the virus is found inconstantly. The cerebral cortex is not a favorable site for survival of the virus which tends within a few days to disappear altogether from the site of inoculation. If the virus travels chiefly by way of the axis cylinders, its appearance in the cerebrospinal fluid would not be expected, nor, in fact, is it found there except on rare occasions.

AUTHOR'S SUMMARY.

SPONTANEOUS TUBERCULOSIS IN THE GUINEA-PIG. A. STANLEY GRIFFITH, J. Path. & Bact. **33**:153, 1930.

Spontaneous tuberculosis in the guinea-pig may be the result of infection with bovine, human or avian tubercle bacilli.

AUTHOR'S SUMMARY.

THE THERMAL DEATH-RATE OF THE BACTERIOPHAGE. SCHRAB H. NANAVUTTY, J. Path. & Bact. **33**:203, 1930.

The mode of destruction of the bacteriophage at different temperatures has been observed and represented graphically in the form of curves. The shape of these curves is consistent and suggests that the bacteriophage is composed of living units having varying susceptibilities to heat. The heat susceptibility of the bacteriophage has been found to be dependent in a large measure on the substrate in which it is suspended, perhaps owing to an alteration in its physical state.

AUTHOR'S SUMMARY.

VACCINATION ENCEPHALITIS. A. ECKSTEIN, H. HERZBERG-KREMMER and K. HERZBERG, Deutsche med. Wschnschr. **56**:264, 1930.

Smallpox virus was found in the blood of eight children between the third and tenth days after vaccination with reaction, and absent from the blood of nine others. None of the spinal fluids obtained from children contained virus, even when the virus could be demonstrated in the blood. The spinal fluid of one of three infants with symptoms of encephalitis produced by the vaccine contained virus on the twelfth day.

PAUL J. BRESLICH.

PRIMARY ACTINOMYCOSIS OF THE STOMACH. HELMUTH NATHAN, Virchows Arch. f. path. Anat. **273**:480, 1929.

A man, aged 46, died of heart failure after an atypical severe stomach disease of a few months' duration. He had hematemesis and lost weight rapidly. Roentgen examination suggested ulcer of the stomach with perforation into the liver. Total acidity was 30; free hydrochloric acid, 15. The diagnosis was carcinomatosis, but the clinicians expected something unusual. Autopsy revealed a large perforated ulcus callosum covered by the liver, duodenum and pancreas. There were abscesses in the liver, pylephlebitic, and there was thrombophlebitis of the hepatic vein with abscesses in the lower lobe of the right lung. The latter observation indicated something unusual, since ordinary infections are stopped by the liver. Smears from the aforementioned foci contained filaments with true dichotomies; anaerobic culture yielded a pure streptothrix. Fungus filaments and sulphur grains were found in the tissues and in the lumen of the blood vessels. There was no typical actinomycotic granulation tissue, only abscesses; but many Russel bodies were found which are considered characteristic for actinomycosis. Probably the existing ulcer was secondarily invaded by the actinomyces. Few certain cases of actinomycosis of the stomach are reported in the literature.

ALFRED PLAUT.

Immunology

THE SEROLOGIC AND ETIOLOGIC SPECIFICITY OF THE ALPHA STREPTOCOCCUS OF GASTRIC ULCER. EDWARD WATTS SAUNDERS, Arch. Int. Med. **45**:347, 1930.

The following facts have been established which demonstrate clearly the specificity of the alpha streptococcus obtained from gastric ulcer: the proof obtained by experiment that a nonhemolytic streptococcus of the alpha type, isolated from nine resected gastric, duodenal and gastrojejunal ulcers, was an agglutinogenic and antigenic homolog; its agglutinogenic and antigenic unlikeness with all alpha strains from foci of infection such as the teeth; its agglutinogenic and antigenic identity with four alpha strains obtained from four cases of an acute specific disease, characterized by small ulcers of the lip, tongue, buccal membrane and tonsils; their relation to alpha prime strains producing ulcers of the skin; their specific agglutination with serums from patients with proved gastric, duodenal

or gastrojejunal ulcers controlled against serums from patients with other types of streptococcus infection; the organisms' apparent presence in the lesion in immediately prepared Levaditi tissue sections; the ability to produce ulcer and its relation to an alpha-prime strain definitely producing ulcer. The possibility of their source being cow's milk has been suggested. If in a large series of cases specific agglutination of the gastric alpha strain continues, as it gives every indication of doing, this department's efforts will be aimed primarily toward determining its source and prevention, and secondarily toward a real vaccine therapy.

AUTHOR'S SUMMARY.

CUTANEOUS REACTIONS WITH CULTURE FILTRATES OF THE COLON TYPHOID TYPE. E. E. ECKER and H. WELCH, J. Exper. Med. **51**:409, 1930.

The observations of Ecker and Rimington on the production of skin reactions with synthetic medium culture filtrates (concentrated and dialyzed) of organisms belonging to the colon-typhoid group have been confirmed and extended. The filtrates show a marked degree of thermostability and marked resistance to ultraviolet radiation. Intravenous injections of the filtrates stimulate the production of precipitins. No precipitins are produced in the serums of rabbits that receive intracutaneous injections only. At no time during the course of immunization was the skin reaction obliterated. An indurative process was noted at the site of injection (skin) during the course of immunization. Mixtures of the filtrates with their homologous antiserums, obtained from animals immunized by the intravenous route, and injected into skin, also failed to obliterate the erythema and edema. The observations of Shwartzman have been confirmed; the Shwartzman phenomenon appears to be group or species specific. Filtrates from enterococci failed to produce the phenomenon. Filtrates of other unrelated organisms have not been studied. The products of Shwartzman and of Ecker and Rimington appear to be the same.

AUTHORS' SUMMARY.

CHANGES IN HUMORAL IMMUNITY OCCURRING DURING THE EARLY STAGES OF EXPERIMENTAL PNEUMOCOCCUS INFECTION. EDWARD E. TERRELL, J. Exper. Med. **51**:425, 1930.

A study was made of the changes in humoral immunity occurring during the early phases of experimental pneumococcus infection in the dog and cat. The methods devised by Robertson and Sia were employed to demonstrate the presence of antipneumococcus properties in the serum of animals naturally resistant to this micro-organism. It was found that with a generalized and overwhelming infection accompanied by early invasion of the blood, there was a prompt and rapid decrease in the concentration of natural humoral immune bodies which frequently disappeared entirely by the time of death. This same early diminution of humoral immune substances, opsonins, agglutinins and pneumococcidal-promoting bodies was observed in animals that survived a moderately severe generalized infection, but the concentration of immune bodies rose again with the onset of recovery. The decrease in concentration of humoral immune substances during a severe generalized infection appeared to be due to the combination of "S" substance with the normal immune bodies. When the pneumococcus infection was more localized as in the case of true lobar pneumonia, a different sequence of events was observed to occur. Several animals, in which extensive lobar pneumonia was produced, showed the presence in quantity of humoral immune bodies in the blood throughout the course of an infection terminating fatally. These observations suggest that after the inception of pneumococcus infection in the dog and cat, the chief function of natural antipneumococcus substances in the blood is to limit or prevent invasion of the blood. When pneumococcic infection is located, these circulating antibodies appear to have little effect either in preventing the spread of the process or in determining the outcome of the disease.

AUTHOR'S SUMMARY.

REACTIONS OF RABBITS TO INTRACUTANEOUS INJECTIONS OF PNEUMOCOCCI AND THEIR PRODUCTS. LOUIS A. JULIANELLE, J. Exper. Med. **51**:441, 449, 463, 1930.

Sixty rabbits were immunized by repeated injections into the skin of small doses of suspensions of heat-killed type I pneumococci. In fifty-three of the rabbits no type-specific antibodies appeared in the serum, and in those remaining the titer of these antibodies in the serum was low. In all cases, however, the serums possessed a high titer of species-specific antibodies. Forty-five rabbits similarly immunized by injections of heat-killed type III pneumococci also failed to form type-specific antibodies but did form species-specific antibodies. Suspensions of heat-killed R pneumococci and solutions of bacterial substances when injected into the skin stimulated the production of species-specific antibodies, although they failed to stimulate the production of any type-specific antibodies. Animals which had been immunized by intracutaneous injections still possessed the ability to form type-specific antibodies when they were subsequently given intravenous inoculations of type-specific pneumococci. Injection of suspensions of heat-killed pneumococci into the skin of rabbits is followed by an active immunity which is effective against intravenous infection by homologous and heterologous types of pneumococcus. This form of active immunity may be induced by the injection of S or R strains of pneumococcus. Intracutaneous immunization with soluble derivatives of pneumococcus does not induce active immunity to infection. The serums of 79 per cent of the rabbits immunized to type I pneumococcus by intracutaneous injections afforded no protection to mice against infection with pneumococci. None of the serums of rabbits intracutaneously immunized to the type-specific type III (S) pneumococci, to R cells or to soluble derivatives of pneumococcus protected white mice against infection. The serums of rabbits immunized first intracutaneously and subsequently intravenously possess a high titer of protective antibodies. It may be concluded that when type-specific pneumococci are injected into the skin, they lose the property of stimulating an active immunity of a specific type and of stimulating the production of type-specific antibodies, but they act just as do the degraded or R forms, causing the animals to become resistant to infection with pneumococci of all types without the development of any type-specific antibodies in the serum. Following repeated intracutaneous injections of heat-killed pneumococci, rabbits acquire an increased skin reactivity. The increased skin reactivity reaches a maximum after from four to six injections have been made, after which it becomes greatly diminished. The relationship of increased skin reactivity to active resistance to infection by pneumococcus, and to the presence of species-specific antibodies in the blood, is still obscure. The increased skin reactivity is not transferable by serum from a highly reactive to a normal rabbit. After regression of the reaction to the first injection of pneumococcus into the skin, there frequently follows a recrudescence, or exacerbation, of the reaction. The increased skin reactivity and secondary reactions are incited alike by all types and all forms of pneumococcus.

AUTHOR'S SUMMARY.

ON THE INHERITANCE AND RACIAL DISTRIBUTION OF AGGLUTINABLE PROPERTIES OF HUMAN BLOOD. K. LANDSTEINER and PHILIP LEVINE, J. Immunol. **18**:87, 1930.

The studies reported substantiate the view that an agglutinable property of human blood detected by an agglutinin present in certain exceptional human serums ("extra agglutinin I") is inherited and that its frequency shows a racial difference in the two populations examined. Consequently, it must be considered as a constitutional property. The same conclusion seems to hold for other properties of red cells demonstrable by atypical human serums. Evidence is presented

to show that the qualities characterizing the two subgroups of group A are inherited. The experiments reported were made with the use of some atypical serums containing agglutinins of marked activity.

AUTHORS' SUMMARY.

THE RATE OF DISAPPEARANCE OF INJECTED HORSE SERUM FROM THE BLOOD OF THE RABBIT. H. R. DEAN, N. E. GOLDSWORTHY and C. TEN BROECK, J. Immunol. **18**:95, 1930.

A series of rabbits have received intravenous injections of horse serum, usually 10 cc. Samples of blood have been taken from these rabbits at intervals from a few minutes to twelve days after the injection. The volume of horse serum present in the rabbit serum obtained from these samples has been determined by the optimal proportions method. The blood volume of each rabbit has been calculated by a formula put forward by G. Dreyer and W. Ray (1912), and the serum volume has been taken as 60 per cent of the blood volume. The results obtained by the titration of each sample together with the calculated serum volume of the rabbit provide data for the estimation of the volume of horse serum present in the blood of the rabbit at various intervals after the injection. In a considerable proportion of the experiments the results obtained during the first hour after the injection have yielded ridiculously high figures, results indeed which appeared to show that the rabbit's blood contained more horse serum than had in fact been injected. In other experiments the results obtained from the titration of the earlier samples were more reasonable. A satisfactory explanation of the more surprising results has not been found. In all experiments the rate of disappearance of horse serum from the blood of the rabbit was rapid during the first six hours, after which on an average about 50 per cent of the horse serum that had been injected had disappeared. After the sixth hour the rate of disappearance was much more gradual. Quantitative determinations of the volume of the horse serum which remained in the rabbit's blood could be made until about the eighth day, when rather less than 10 per cent of the injected volume of horse serum remained.

AUTHORS' SUMMARY.

SKIN REACTIONS PRODUCED BY ANTIHUMAN SERUM. WILLIAM W. REDFERN, J. Immunol. **18**:109, 1930.

A pronounced twenty-four hour local reaction follows injection of rabbit antihuman serum into human skin. This reaction is almost identical with that produced by a second injection of antigen into a previously sensitized local area. Microscopically, both are seen to be inflammatory, showing edema and perivascular round cell infiltration. Fractionation of immune serum with ammonium sulphate shows that the skin reactive substances are closely associated with the globulins as are also the precipitins. Removal of the precipitins, however, fails to destroy the skin reacting properties. The albumin fraction of rabbit serum fails to incite an immediate urticarial reaction in human skin as does the globulin. Persons who show clinical manifestations of hypersensitiveness do not show stronger skin reactions than nonsensitive persons. Five patients from the series of sixty-eight given injections showed a local delayed reaction comparable to that of serum sickness.

AUTHOR'S SUMMARY.

ALLERGIC TESTIS REACTIONS IN GUINEA-PIGS WITH COCCIDIOIDAL GRANULOMA. EDWIN F. HIRSCH and DOROTHY D'ANDREA, J. Immunol. **18**:121, 1930.

The testes of guinea-pigs with coccidioidal granuloma respond to injections of broth culture filtrates of *Coccidioides immitis*, as do other allergic tissues in the presence of antigen, by the appearance of an acute inflammatory exudate far

in excess of that in the tissues of uninfected hosts similarly injected. These results are further evidence that the tissue reactions of hosts with coccidioidal granuloma, when culture filtrates of *Coccidioides immitis* are injected, are allergic.

AUTHORS' SUMMARY.

THE RELATIONSHIP OF TWO HEMOTOXIC ANTIGENS IN B. WELCHII GROWTH PRODUCTS. A. F. SCHNAYERSON and S. L. SAMUELS, J. Immunol. **18**: 141, 1930.

In the sterile filtrates of *B. welchii* broth cultures, two hemotoxins have been demonstrated. One of these designated as A is active in vitro and probably to some extent in vivo; the other, B, causes no hemolysis in vitro but marked blood destruction in vivo. These two principles were not completely separated. The hemotoxin A (hemolysin) was produced in such strength that 0.0075 cc. completely lysed 1 cc. of 5 per cent washed red blood sheep cells in eighteen hours. Hemotoxin B was generally found to be much more toxic for pigeons than A. Immune serums were produced with these two hemotoxins. It was found that antihemotoxin A serum in high dilution would neutralize its homologous antigen whereas antihemotoxin B had no effect on it. On intravenous inoculation into rabbits it has been found that hemotoxin B alone caused approximately as marked an anemia as a mixture of A and B. Although A apparently gave rise to a more rapid initial hemolysis in vitro than B, the continuing anemia and morphologic blood changes were evidently due to the action of hemotoxin B.

AUTHORS' SUMMARY.

THE NATURE OF THE SO-CALLED CONGLUTINATION REACTION (BORDET-STRENG). HARRY EAGLE, J. Immunol. **18**:169, 1930.

The adsorption (fixation) of complement midpiece by antigen-antibody suspensions (sensitized red cells or bacteria; specific precipitate) causes a change in their surface properties, evidenced by an increased tendency to cohesion and flocculation. So-called conglutination is a specific instance of this general property of complement-midpiece, involving sensitized cells and the slight quantities of midpiece present in heated serums. Since the terms conglutinin and conglutination do not define a distinctive substance or reaction, it is suggested that they be dropped from immunologic nomenclature.

AUTHOR'S SUMMARY.

EFFECT OF SODIUM CITRATE ON ANTIPNEUMOCOCCUS POWERS OF BLOOD. SHEO NAN CHEER, J. Immunol. **18**:187, 1930.

The concentrations of sodium citrate which were found to be without detectable deleterious action on the pneumococcidal properties of the blood elements are considerably less than those customarily employed in citrated blood transfusions.

AUTHOR'S SUMMARY.

A SKIN TEST FOR SUSCEPTIBILITY TO SMALLPOX. SANFORD B. HOOKER, J. Infect. Dis. **45**:255, 1929.

Endermal injections of heat-killed vaccine virus produce definite and easily interpretable reactions which are rather highly dependable as indexes of immunity to smallpox, correlating well with the various grades of response to living virus. The few discrepant reactions have been on the "false" positive side and are probably ascribable to other proteins which contaminate crude virus; the negative reaction as a criterion of susceptibility has so far been wholly reliable.

AUTHOR'S SUMMARY.

BIOLOGIC RELATIONSHIPS OF MORGAN'S BACILLUS AS SHOWN BY COMPLEMENT FIXATION. LEON C. HAVENS and CATHERINE RIDGWAY, J. Infect. Dis. **45**:263, 1929.

Complement-fixation reactions between ten strains of *Bacillus morgani* revealed close antigenic identity. The serologic unity demonstrated by this method permitted a study of the antigenic relationship of *B. morgani* to members of the typhoid-dysentery group. Close relationship to the paratyphoid and paradysentery strains studied was indicated. The paratyphoid and paradysentery serums reacted with *B. morgani* antigens in the same manner and degree as did the Morgan serums. The same relationship held true for the Morgan serums and the paratyphoid and paradysentery antigens.

AUTHORS' SUMMARY.

AMMONIUM SULPHATE PRECIPITATION OF TOXIC SUBSTANCES OF BACILLUS TYPHOSUS. GREGORY SHWARTZMAN, J. Infect. Dis. **45**:283, 1929.

In this work, filtrates of washings of a twenty to a twenty-two-hour-old growth of *Bacillus typhosus* on plain agar were fully saturated with ammonium sulphate. The precipitates and precipitate-free filtrates were tseted in rabbits. There were no skin preparatory or reacting factors detected in precipitate-free filtrates even in amounts representing several multiples of the minimal doses necessary to elicit the phenomenon with the untreated "mother" filtrates. The precipitate-free filtrates showed no general toxicity for rabbits. The precipitates, on the other hand, contained both powerful skin preparatory and reacting factors. A yield of 9.1 Gm. of dry powder was obtained from 4,000 cc. of the "agar-washings" filtrates after precipitation and dialysis. When both the skin and intravenous injections of the precipitate were made into the same rabbits, 0.1 mg. was sufficient to prepare the skin of some rabbits which subsequently received 8 mg. per kilogram of the precipitate intravenously. When, however, the intravenous dose was reduced to 2 mg. of precipitate per kilogram, it was necessary to use 1.0 mg. intradermally in order to prepare for the reaction. Doses of the precipitates larger than 2 mg. per kilogram injected intravenously often produced general toxicity. The potency of the precipitate, preserved over phosphorus pentoxide in a desiccator at room temperature, remained unchanged for four and seven months after its preparation was completed.

AUTHOR'S SUMMARY.

SEROLOGIC SPECIFICITY OF STREPTOCOCCI HAVING EFFECTIVE LOCALIZING POWER AS ISOLATED IN VARIOUS DISEASES OF MAN. EDWARD C. ROSENOW, J. Infect. Dis. **45**:331, 1929.

A large number of strains of green-producing streptococci have been studied serologically with hyperimmune serums prepared with the respective freshly isolated strains of streptococci. These streptococci had been isolated directly from patients having various diseases, or more often from the tissues showing specific lesions in animals following injection of freshly isolated cultures of streptococci having elective localizing power. Both the precipitin and agglutinin reactions were used and gave comparable results. In these serologic experiments, it was found that although the streptococci isolated in widely different diseases are much alike culturally and morphologically, they react differently serologically. All or most of the different strains isolated in each of the following diseases reacted specifically with the corresponding antiserums: those of poliomyelitis, encephalitis, chorea, influenza, epidemic parotitis, ulcer of the stomach or duodenum, ulcerative colitis, cholecystitis, chronic arthritis, pyelonephritis and endocervicitis. The strains isolated in a study of similar diseases were found more closely related serologically than those isolated in a study of more widely different diseases. Thus, from poliomyelitis and encephalitis the strains were the most nearly alike of any that were studied. These and the chorea strains were next most closely related. The

arthritic and spasmodic torticollis strains were more like the chorea strains than like the encephalitis, poliomyelitis and other strains. Arthritis is common in spontaneous chorea, and chorea strains often produce arthritis in animals on intravenous injection; the symptoms in animals following intracerebral injection of spasmodic torticollis and chorea strains are strikingly similar. The strains from respiratory arhythmia, a disease always associated with symptoms of encephalitis, were found more closely related to encephalitis strains than to the poliomyelitis and chorea strains. Hemolytic streptococcus antiserums, from septic infections and scarlet fever, reacted specifically with the respective strains but not with the hemolytic streptococci isolated in epidemic influenza. This indicates that the hemolytic streptococci so often encountered in epidemic influenza are not merely invaders of *Streptococcus pyogenes* from the upper respiratory tract. Serologic specificity (just as elective localizing power) is usually lost rather soon after artificial cultivation but not in a parallel manner. Both serologic specificity and elective localizing power usually can be maintained for many culture generations if transfers (0.2 cc.) are made often (from four to eight times a day) in previously warmed dextrose-brain broth (15 cc. amounts in tall 12 cm. columns). Specific antigenic properties were best maintained by keeping cultures in latent life in meat infusion, on blood agar slants sealed with paraffin corks, and in dense suspension in glycerol and sodium chloride solution. Marked changes occurred in some strains regardless of the various methods employed to maintain specificity. These will be considered in a separate paper. The secret of being able to prepare these highly specific antiserums rests, aside from proper dosage and so forth, largely on the use as antigens, during the prolonged period of immunization, of the respective strains which, at the time when they had been freshly isolated, had been placed for preservation in dense suspension in glycerol and sodium chloride solution. Positive precipitin and agglutinin reactions were obtained more often with heterologous strains of green-producing streptococci and the different green-producing streptococci antiserums than with strains of type pneumococci and hemolytic streptococci. This fact indicates that the different green-producing streptococci isolated in a study of the different diseases, while they seem highly specific when tested under selected laboratory conditions, yet are much alike basically. The close relationship, basically, between the different groups of green-producing streptococci was further shown by the fact that the serum of horses that reacted highly specifically after a short period of immunization acquired increasing precipitating and agglutinating power over nonspecific strains after prolonged immunization. This occurred when the precipitating or agglutinating power over the specific strains was no higher or even when it was lower than during the earlier part of the period of immunization. This observation suggests that perhaps antiserums might be prepared from a single strain or group of strains of green-producing streptococci which would have beneficial therapeutic effects in widely different diseases due to green-producing streptococci. The results from the serologic study support those obtained from studies of elective localization, and the conclusion that the various strains isolated in a study of the different diseases are of etiologic importance seems warranted. Since most of the strains from each of the different diseases are serologically much alike, or identical, and since all possess well marked antigenic power, it may be hoped that attempts at the preparation and use of specific antiserums in treatment, now under way, will prove of value in all of the diseases studied, as have those in poliomyelitis, encephalitis and ulcerative colitis.

AUTHOR'S SUMMARY.

ON THE CONCENTRATION OF ANTISTREPTOCOCCUS SERUM. GEORGE F. FASTING, J. Infect. Dis. **45**:360, 1929.

A modification of the Felton method for precipitating antibody-euglobulin in antistreptococcus serums has been described. The use of ether in the diluent, for lowering surface tension, appears to have technical advantages and does not destroy the therapeutic merits of the antibody-euglobulin. The antibody fraction has been

administered intramuscularly and subcutaneously in a large number of cases, over a long period of time, without the observation of the complications and undesirable features of whole serum or of that concentrated by the salting method. Prolonged immunization of horses with green-producing streptococci produces a change in the euglobulin. This change is manifested by the appearance and increase of a fraction with an iso-electric point near that of normal blood, which carries down the bulk of the agglutinin and other antibodies, and which is of definite therapeutic value.

AUTHOR'S SUMMARY.

ANAPHYLACTIC SENSITIZATION OF GUINEA-PIGS TO STREPTOCOCCAL FILTRATES AND TO UNINOCULATED BROTH. JEAN V. COOKE, J. Infect. Dis. **45**:435, 1929.

Under certain circumstances the injection of nutrient broth into guinea-pigs produces specific anaphylactic hypersensitivity which may be shown by the Schultz-Dale method. Broth filtrates of bacteria, therefore, cannot be used to demonstrate the presence of specific bacterial antigen by this method for testing for allergic hypersensitivity.

AUTHOR'S SUMMARY.

THE COMPARATIVE POTENCY OF CONCENTRATED AND UNCONCENTRATED ANTIPNEUMOCOCCUS SERUM. GRACE M. SICKLES, J. Infect. Dis. **45**:490, 1929.

Previous experience with the testing of various concentrated and unconcentrated antipneumococcus serums is summed up, and results are recorded with two samples of the more recent preparations of concentrated antipneumococcus antibody solution which were tested against a virulent strain of pneumococcus type I by the Felton method. With the strain of pneumococcus used, the estimated titer of both samples was lower than that with which they were labeled. The estimated titer of an unconcentrated serum of high potency, tested by this method, was not materially lower than that of the concentrated products. In tests in which large amounts of culture and serum were used the unconcentrated serum, because of the so-called zone phenomenon, appeared to be superior to the concentrated product.

AUTHOR'S SUMMARY.

THE CONTENT OF ANTIBODIES IN BLOOD PLASMA AND IN SERUM. R. S. TSCHERIKOWER and F. T. GRÜNBAUM, Zentralbl. f. Bakteriol. **112**:108, 1929.

The authors tested the content of antibodies in the same animal as to concentration in the plasma, serum from clotting and serum from defibrinated blood. They did this because of observations by Kritschewski and Tscherikower (*Ztschr. f. Immunitätsforsch. u. exper. Therap.*, 1925, vol. 42) that thrombocytobarines are in less concentration in serum from clotted blood than in defibrinated serum from the same blood. The concentration of thrombocytobarine and bacterial agglutinin was greater in defibrinated blood than in plasma or in serum from clotting, and was greater in plasma than in serum from clotting in the case of thrombocytobarine. Similar results were obtained with bacteriolysin and hemolysin. The hemagglutinins and precipitins, however, were in higher concentration in the plasma. In the latter case, however, when the fluids were diluted and tested with a constant quantity of antigen, the plasma showed the highest titer, whereas when the antigen was diluted, the highest titer was found in the serum from clotting.

PAUL R. CANNON.

THE FLUCTUATION OF THE NORMAL AGGLUTININS AND PRECIPITINS IN THE BLOOD OF GRAVID AND PUERPERAL WOMEN. T. SATO and Y. KATSU, Jap. J. Obst. & Gynec. **12**:152, 1929.

The patients selected for this study were free from any puerperal morbidity and never had had typhoid infection. The serum was titrated with strains of

typhoid bacilli. In general, it was found that in early pregnancies there was a variable range with a more or less decrease in agglutinins, which then gradually increased and by the eighth month approximated that found in the nongravid woman. This increase progressed, being greatest shortly after labor, though the difference of agglutinin titer before and after the birth of the child was not marked. During puerperium there was a gradual decrease to the level of that in the nongravid state. The precipitins did not appear to vary in any peculiar way during pregnancy.

A. J. KOBAK.

Tumors

SARCOMA OF THE VAGINA. S. E. TRACY, Am. J. Obst. & Gynec. **19**:279, 1930.

This is a rare form of tumor that occurs most frequently in the first four decades of life. The author quotes McFarland's 1911 collection of 102 cases, who found that thirty-four of forty-four cases that occurred in the first five years were sarcoma botryoides. Tracy adds four of his own cases, all in adults, three of which were in the third and one in the fifth decade. These tumors arose from the rectovaginal and vesicovaginal septums of the vagina. Two were of the round cell, one of the spindle cell and a fourth of a mixed cell type. Sarcoma of the vagina is a rapid and hopelessly recurring type of tumor. The spindle cell sarcoma, however, has survived for six years after the use of 2,400 milligram hours of radium, following surgical enucleation.

A. J. KOBAK.

PRIMARY CARCINOMA OF THE LUNG. JAMES ALEXANDER MILLER AND OSWALD R. JONES, Am. Rev. Tuberc. **21**:1, 1930.

The authors report thirty-two cases of primary carcinoma of the lung observed during the past six years, the diagnosis in each being substantiated by either bronchoscopic or postmortem sections. In addition, the clinical diagnosis of primary bronchial carcinoma was made in more than 100 other cases in which the authors were unable to obtain a section of tissue. This experience is testimony to the relative frequency of the condition.

H. J. CORPER.

NEOPLASMS OF THE LUNG. WILLIAM C. VON GLAHN, Am. Rev. Tuberc. **21**: 57, 1930.

Seven cases with autopsy are reported. The cases of carcinoma are divided into those arising in primary bronchi, in tuberculous foci, in alveolar epithelium and in bronchiectatic cavity. The author doubts that there has been an actual increase in carcinoma of the lung.

H. J. CORPER.

A STATISTICAL STUDY OF THE COINCIDENCE OF MALIGNANCY AND TUBERCULOSIS. CARL H. FORTUNE, Ann. Int. Med. **3**:495, 1929.

Fortune carried out a controlled statistical analysis of the coincidence of malignancy and tuberculosis based on the autopsy records of the department of pathology of the University of Michigan. This study revealed that active tuberculosis occurs neither more nor less frequency combined with malignancy that it does combined with any other major disease capable of producing death. Healed tuberculosis was found to occur with approximately equal frequency in cancerous and noncancerous persons.

WALTER M. SIMPSON.

GELATINOUS CARCINOMA OF THE BREAST. G. L. CHEATLE and M. CUTLER, Arch. Surg. **20**:569, 1930.

Gelatinous carcinoma is comparatively rare. Forty-nine instances were found in 2,944 cases of carcinoma of the breast. The amount of gelatinous material may

vary. Sometimes the tumor reaches enormous size. The gross features are striking. The tumor may be easily recognized by the light gray, jelly-like substance. Microscopically, these tumors have the usual appearance of carcinoma, usually of the scirrhous type, with, in addition, a large amount of gelatinous material and degenerating islets of tumor tissue. Two points of view are held as to the origin of the gelatinous substance. Some believe that it takes origin in the stroma and others from the epithelial cells. Various authors have reported comparatively slow growth of these tumors. Recurrences appear late, and the results of operation are generally better. Nevertheless, these tumors may be quite malignant. The amount of colloid substance may be so extensive as to make it difficult to find the tumor-bearing areas. From the examples described, there seems to be no doubt that the gelatinous material takes origin in the neoplastic epithelium. Gelatinous degeneration is more common than is generally supposed, and may often be overlooked, particularly if only a few sections are taken of the specimen. The process begins and ends in the epithelium. Gelatinous deposits may also be found in the metastases.

N. ENZER.

RECURRENT SO-CALLED GIANT CELL TUMOR. C. F. GESCHICKTER and M. M. COPELAND, Arch. Surg. **20**:713, 1930.

The authors present a review of a series of giant cell tumors which have been reported to have recurred or to have become malignant. In the groups examined clinically there were twenty-six that recurred after primary curettement. Studies of those groups indicate that the recurrence was not due to any inherent quality in the tumor, but rather to a poor selection of the type of treatment, or else to incomplete operation. The microscopic lesions in this series did not show any peculiarities which would account for their recurrence. Thus, they contained large numbers of multinucleated giant cells in the primary tumor, and there was no structural change which could be considered sarcomatous in the recurrent tumor. The recurrent lesion is usually characterized by an increase in fibrous tissue and in fibroblasts. Occasional large xanthoma cells are found, and these are considered the result of perforation of the bony capsule and extension of the tumor into the soft tissue, which would furnish the lipoids characteristic of these cells. In 105 cases in which the patient submitted to primary curettement, the ages of those in whom curettement was successfully done were as follows: 21 per cent were over 30 and 41 per cent were under 21. In the recurrent tumors, 42 per cent were over 30 and only 16 per cent under 21.

The lower end of the radius appears to be a favorable location for the return of the lesion after curettement. The upper part of the tibia showed relatively few recurrences and the lower part of the femur a moderate number. Recurrence may be due to the destruction of the bone shell in the nonweight-bearing bone before attention is drawn to the lesion. Recurrence occurred more often after curettement than after resection. In this series giant cell tumor did not recur after a primary radical operation.

The second group of cases included those that were reported to have malignant variants and certain differential points in the microscopic pictures. Infection is often the cause of a change in the structure, which may be mistaken for a sarcomatous change. Often, also, the healing process is mistaken for a malignant variant. The apparent malignant modification in the microscopic structure of giant cell tumor is usually the result and not the cause of the recurrence. When the malignant variant is present in the primary tumor and recurrence results, metastasis is apt to follow, and this tumor must be considered as an osteogenic sarcoma and not a giant cell tumor. In the reported cases of metastatic giant cell tumor, the authors find that the metastatic nodule did not have the structure of giant cell tumor and that the metastases are always definitely sarcomatous. They have analyzed these cases, and have shown that the primary lesion is really a sarcoma with giant cells and not essentially a giant cell tumor.

N. ENZER.

GAS SECRETION IN GASTRIC CANCER. W. S. POLLAND and A. L. BLOOMFIELD, Bull. Johns Hopkins Hosp. **46**:307, 1930.

Most cases of cancer of the stomach show a deficient gastric juice as evidenced especially by abnormally small volumes of secretion with a low acidity or with an absence of acid. In a small proportion of the cases there are secretory observations within normal limits. Cancer appears to arise almost always on the basis of an already existing lesion, usually a chronic gastritis, less frequently a peptic ulcer.

AUTHORS' SUMMARY.

RELATIVE POTENCY OF CARCINOGENIC TARS AND OILS. C. C. TWORT and J. M. TWORT, J. Hyg. **29**:373, 1930.

A method has been devised whereby the potency of any given carcinogenic agent can be compared with that of a standard agent. This is called the standard carcinogenic potency of the agent (P). The relative potency of the agent (R P), calculated from P, permits one to estimate the effect on the agent of different chemical treatments and dilutions, the percentage increase or decrease in activity of the agent being at once shown. A unit of carcinogenicity (U. C.) has been established, and a concentration of 500 carcinogenic units per cubic centimeter is considered to induce the maximum relative response in animals when the agent is applied twice a week.

PRIMARY CARCINOMA OF THE LUNG. S. L. SIMPSON, Quart. J. Med. **22**:413, 1929.

This article is based on a study of 139 patients with carcinoma of the lung admitted to the London Hospital between 1907 and 1925. The author devotes considerable space to the consideration of so-called "oat-cell sarcoma," a rather unfortunate term. He believes that these tumors are really carcinomas, and that practically all of them arise from the bronchi. These tumors differ somewhat in their gross appearance from the more characteristic carcinomas of the lung. They tend to invade the mediastinum more extensively and are subject to more necrosis. However, microscopically, these tumors show considerable pleomorphism; the reverse is also true, namely, areas of oat cells may be found in large celled carcinoma. The metastases occurred most frequently to the regional glands, liver, vertebrae, ribs and brain. Pleural effusion occurred in thirty-nine cases, and various types of inflammatory reaction were found within the lung. The pericardium was invaded in sixty-two instances, twenty-one of which were associated with pericardial effusion. Thrombosis was common, and direct invasion of the superior vena cava occurred in sixteen cases. The errors of diagnosis are rather interesting. Of the 108 cases, sixty-six were incorrectly diagnosed. These were divided into: (1) the pulmonary group, in which there were twenty-four cases in which such diagnoses as pleural effusion, bronchopneumonia, bronchiectasis, etc. were made; (2) the cerebral group consisting of thirteen cases, in which such diagnoses as cerebral neoplasm, abscess, encephalitis, etc., were made, and (3) the spinal group of five cases, in which the diagnoses made were transverse myelitis, paraplegia and caries of the spine. In five instances the diagnosis was aneurysm, and in nineteen there was a multiplicity of wrong diagnoses such as gastric ulcer, carcinoma of the esophagus, generalized carcinoma, etc. These diagnoses are analyzed in detail, the source of error being indicated. There were nine cases incorrectly diagnosed during the life of the patient as carcinoma of the lung, which on postmortem examination proved to be lymphogranuloma, carcinoma of the thyroid, carcinoma of the thymus, lymphogranuloma of the thymus, fibrosarcoma of the mediastinum and carcinoma of the nasopharynx.

The author discusses the alleged increase in the incidence of primary carcinoma of the lung and reviews the literature. From his own investigations he concludes that there is a real increase in the incidence of pulmonary carcinoma, and this

increase is beyond the increase in carcinoma in general. With regard to the etiology, he is inclined to believe that there is some irritative factor. There seems to have been an increase following the influenza epidemic of 1918, and there is a high incidence of pulmonary infection preceding the onset of the tumor. Increase in carcinoma of the lung in Saxony is reviewed, and he points to the possible sources of inhaled irritants such as tar, bismuth, arsenic and cobalt. There seems to be less evidence in favor of tuberculosis being an etiologic factor than was previously supposed. Likewise, syphilis does not seem to bear any direct relationship.

N. ENZER.

SUPRARENAL VIRULISM. A. D. FORDYCE, Quart. J. Med. **22**:557, 1929.

The author reports two cases of hypernephroma in the cortex of the suprarenal with virulism, one in a boy and one in a girl. The case histories and pathologic descriptions are complete. No chromatin tissue could be recognized in either specimen.

N. ENZER.

REACTION OF THE STROMA TO CARCINOMA. R. BÖHMIG, Beitr. z. path. Anat. u. z. allg. Path. **83**:333, 1929.

Ribbert, who considered chronic inflammation an important factor in the genesis of carcinoma, looked on the reactions manifested by the stroma, in and about the tumor, and especially the round cell infiltration, as primary changes leading to the formation of the neoplasm. Borst held these reactions to be the expression of local disturbances of metabolism. Many pathologists have believed them to be inflammatory and secondary to the presence of the tumor. Experimental tumor transplantation has ascribed an important protective and immunologic rôle to the stroma reaction. Böhmig made a systematic study of 115 carcinomas from human beings, paying especial attention to the stroma within the tumor and at its periphery and to the stroma of the organ at a distance from the tumor. The material utilized, lesions with ulceration being excluded, included thirty-four epitheliomas of the skin and eleven of the cervix uteri, twelve glandular carcinomas of the breast, twenty-three of the stomach and intestine and six of the uterus, fifteen scirrhous carcinomas of the breast, fourteen metastatic carcinomas of the liver and thirty-nine metastases of the lymph nodes. In the microscopic examination, especial attention was paid to the blood vessels of the stroma, to the density, hyalinization and elastic changes of the stroma and to the degree and character of the round cell infiltration of the stroma. The author concludes that the reaction of the stroma cannot be interpreted as either a local or a general immunologic reaction, and that no prognostic deductions may be made from the character of the reaction. The latter is inflammatory and is secondary in origin. Its character depends on the morphologic type of the tumor, and on the preexisting structure of the stroma of the organ.

O. T. SCHULTZ.

ENERGY METABOLISM OF GRANULATION TISSUE. C. NEUHAUS, Beitr. z. path. Anat. u. z. allg. Path. **83**:383, 1929.

Determination of the glycolytic activity and oxygen consumption of tissue under aerobic and anaerobic conditions, by the method of Warburg, has shown that embryonic tissue and tumor tissue, both of which are rapidly growing, differ from each other in that the former has slight or no glycolytic activity under aerobic conditions, whereas tumor tissue readily splits carbohydrates under aerobic conditions. In its growth characteristics, Neuhaus conceives granulation tissue to be intermediate between embryonic and tumor tissue. The growth of embryonic tissue is orderly and is regulated by the needs of the organism as a whole. The growth of tumor tissue is disorderly and autonomic or unregulated. The growth of granulation tissue is a disorderly process, and in this respect granulation tissue

and tumor tissue are alike, but the growth is regulated or controlled by the needs of the organism, and in this respect granulation tissue is like embryonic tissue. To test the correctness of this conception, Neuhaus made a study of the glycolytic activity and respiration of granulation tissue by the method of Warburg. The tissues used were tuberculous granulation tissue of the guinea-pig, foreign body granulation tissue of the guinea-pig and white rat caused by the subcutaneous injection of purified siliceous earth and aseptic callus of the rabbit and dog caused by fracture of the humerus or femur. In its glycolytic activity under aerobic conditions granulation tissue was found to be intermediate between embryonic and tumor tissue. The degree of aerobic glycolysis varied, however, in the different species of animals and to a lesser degree in individuals of the same species. The degree of activity was progressively greater according to species in the following order: dog, guinea-pig, rabbit, rat. The activity of granulation tissue from the rabbit is comparable to that of benign tumor tissue; that of granulation tissue from the rat to malignant tumor tissue. These differences are not due to differences in the disorderly character of the granulation tissue, but to species-specific differences of tissue. The greater the metabolic activity of the granulation tissue of a species, the more prone is the tissue of that species to the formation of tumor.

O. T. SCHULTZ.

CARCINOMA OF THE FOOT AFTER ATROPHY OF THE SKIN. W. KRESSIN, Deutsche med. Wchnschr. **56**:12, 1930.

A white man, aged 68, was treated for years because of ulcers in the atrophic skin of the legs and feet. The ulcers recurred from time to time, but one over the left external malleolus finally failed to heal. Histologically, this ulcer proved to be a squamous cell carcinoma. After high amputation of the leg, metastases were found in the femoral lymph nodes.

PAUL J. BRESLICH.

SEROLOGIC SPECIFICNESS OF CANCER TISSUE. E. WITEBSKY, Klin. Wchnschr. **9**:58, 1930.

Organ suspensions, with the exception of suspension of the lens, usually yield antibodies that are species rather than organ specific. In this respect, there is a difference in the behavior of different organs; brain suspensions, for example, give rise to lipoid antibodies that are organ specific, while mesodermal or endodermal organs usually yield only species specific antibodies. Alcoholic extracts of tumors also are specific for the blood groups, which complicates matters. The injection of alcoholic extracts of carcinoma leads to the formation of antiserums with varied properties. In one series of experiments, extract from ovarian carcinoma yielded an antiserum that reacted specifically with the homologous antigen and gave no reactions with extracts from rectal carcinoma or normal organs. In this case, the antiserum was specific not only for the new tissue but also for the organ in which it formed. In another series, the antiserum was species specific, giving cancer specificity only when the test solutions were first treated with a little lecithin. In still other experiments, the antiserums gave a cancer rather than an organ or a species specificity. Boiled globulins extracted from mediastinal and rectal cancers and from normal liver yielded antiserums that were specific for the homologous antigen. In the case of metastases, the boiled globulins show two kinds of specificity, one for the organ containing the primary carcinoma and the other for the organ in which the metastasis occurred. In some cases, reactions were obtained also by treating the globulin antiserums with suspensions of the homologous carcinoma. Specific antiserums may be obtained by injection of either the alcoholic extracts or the globulins from cancer tissues, the specificity being for the organ in which the cancer resides. The formation of cancer tissue thus results in a new cancer specificity which is different for each organ. The significance of these results for biology and for the serologic treatment for cancer is discussed.

ARTHUR G. COLE.

HISTOCHEMICAL CHANGES IN CARCINOMA FROM RADIUM. L. SCHOENHOLZ and H. HIRSCH, Strahlentherapie **34**:273, 1929.

The study was made on carcinoma of the cervix. There was found a marked increase in calcium in ashed sections of the tissue two days after irradiation, while the structure as revealed in ordinary tissue seemed to be unchanged. The increase in calcium in the carcinoma cells is regarded as due to irradiation and as independent of changes in the connective tissue.

PRIMITIVE HEMANGIOMA OF THE STRIATED MUSCLES. T. ANARDI, Tumori **16**:159, 1930.

The author describes two cases of primary hemangioma of striated muscles (triceps and sternocleidomastoideus), both with phleboliths. The anatomopathologic study of the removed masses is followed by a chemical and histopathologic study of the phleboliths. In the second patient these were found in diverse stages of evolution which made it possible to arrive at any conclusion concerning the development of these formations. AUTHOR'S SUMMARY.

PRIMARY EPITHELIAL BLOOD-FORMING LIVER TUMORS IN SHEEP AND CATTLE (ADENOMA AND ADENOCARCINOMA HEPATOCELLULARE HEMATOPLASTICUM). H. S. FRENKEL, Virchows Arch. f. path. Anat. **273**:611, 1929.

Epithelial tumors of the livers from six sheep were examined. They were all situated in the right lobe, varying in size from that of a hen's egg to that of a child's head. They were mostly soft and medullary and were well separated from the surrounding liver tissue; metastases were present in some, in the liver tissue itself and in the lymph nodes. Some of the tumors had a more trabecular structure, others were more tubular. The outstanding feature was the presence of hematopoietic foci which were conspicuous by the intense staining of the nuclei. The blood formation could be studied in these tumors much better than in the embryonic liver. Hemogones ("Haemogonien"), single and in groups, develop from the endothelium of capillaries. Hemoglobin-containing cells are seen among them. The nuclei of the red cells disappear by lysis or rhexis, never by expulsion. Giant cells seem to spring from the hemogones by amitosis. In spite of the presence of all stages of blood formation no connection between blood-forming cells and epithelium could be found. In some specimens the epithelium and blood-forming tissue seem to be situated very closely together, but reticulum stain indicates that they are separate. The reticulum is similar to that described by Mollier in the embryonic liver.

The blood formation in these tumors is similar to that in the liver of the sheep embryo. The endothelial cell is the common mother cell. The blood formation in these tumors, as well as in the embryonic liver, is autochthonous; the mother cells are furnished by the capillaries of the liver. Extramedullary hematopoiesis in the adult generally takes place within the capillaries. The described extracapillary blood formation is characteristic of these obviously embryonic tumors of sheep and cattle. Five of the six sheep were young. ALFRED PLAUT.

THE NUMBER OF CHROMOSOMES IN HUMAN CANCER CELLS. K. A. HEIBERG and TAGE KEMP, Virchows Arch. f. path. Anat. **273**:693, 1929.

A rapidly growing, not hornifying squamous cell carcinoma in the cheek of an elderly man contained an unusually large number of well preserved mitotic figures. In some of them the chromosomes could be counted. Many were tetraploid (between 90 and 100 chromosomes) and in some there was a still higher number of chromosomes. There were some diploid mitoses, and a few of them were similar to the mitotic figures in normal tissue. In the majority, however, there was an irregular arrangement of chromosomes. Haploid mitoses (twenty-three

chromosomes) could be seen only occasionally. The authors do not want to draw conclusions from the examination of this single tumor. The difficulties lie in the fact that most mitotic figures are too large for complete examination in a single section and that examination of single sections does not give full guarantee of not losing single chromosomes. Furthermore, change in size and shape and possible disintegration of chromosomes may lead to error. Corresponding investigations on tissue cultures will be made.

ALFRED PLAUT.

PRIMARY CARCINOMA OF THE THYMUS. A. PARABUTSCHEW, Ztschr. f. Krebsforsch. **30**:380, 1929.

Four cases of primary carcinoma of the thymus are reported. To warrant such a diagnosis, the author submits the following criteria: absolute exclusion of other possible primary sites, proper location of the tumor, with regard to its relationships to surrounding structures, and histologic character. According to Parabutschew, all forms of these tumors are derived from reticular tissue. Hassall corpuscles, which he regards as degenerative metamorphoses of reticular cells, are not pathognomonic. He regards as an important predisposing factor restricted involution of the organ as a result of inadequate function of the sex glands, which may be accentuated by the pathologic involution of these in advanced age. It may be mentioned incidentally that his cases did not show a high age factor; his patients were aged 42, 54, 49 and 38 years, respectively. He considers these so-called thymomas as representing transitional forms between benign and malignant tumor.

H. E. EGGERS.

THE PRODUCTION OF A GENERAL PREDISPOSITION TO TUMOR. K. AKIMOTO, Ztschr. f. Krebsforsch. **30**:428, 1929.

While the author was unsuccessful in influencing the susceptibility of rabbits resistant to coal tar by the injection of the serum of sensitive animals, he was more successful in obtaining evidence of increased general predisposition by the use of tar itself. He applied it, in rabbits and mice, to skin areas rarely the site of cancer, and traumatized the more usually cancerous areas by burning. With the rabbits, the results were merely suggestive, and took the form of limited epithelial hyperplasia at the sites of the burns. But with the mice, skin tumors developed in the burned areas in those tarred in a percentage of 48, as compared with 20 per cent in untarred controls. Although 64.5 per cent of the tarred animals showed skin tumors at the site of tarring, it was rather evident that the burn cancers were not metastases from these tumors; in many the two tumors developed simultaneously; in some they were of different histologic character, and in some they occurred only at the burned site.

H. E. EGGERS.

VITAMIN DEFICIENCY IN THE CAUSATION OF CANCER. O. L. E. DE RAADT, Ztschr. f. Krebsforsch. **30**:449, 1929.

Since vitamin deficiency, which has been shown to be of etiologic significance in the causation of experimental cancer, cannot be regarded as playing any important part in that disease in man, de Raadt believes that the explanation of its action is to be sought farther, in the alkalosis which results from vitamin A deficiency. In support of this view he cites the frequency of cancer of the liver in the Orient, with its largely vegetarian diet; the low incidence of cancer in tuberculous patients, with their intentionally high protein intake; the rare occurrence of cancer in lepers; the fact that in Italy the distribution of cancer seems to correspond to the dietetic habits of the inhabitants, with a high rate corresponding to the regions of diets low in protein, and the relatively vegetarian diet of the aged.

H. E. EGGERS.

HISTOGENESIS, STRUCTURE AND CHARACTER OF SO-CALLED PLANT CANCER. H. HAMDI, Ztschr. f. Krebsforsch. **30**:547, 1930.

From a careful study of the growth characteristics of the plant tumors resulting from infection with *Bacillus tumefaciens,* the author concludes that these are not akin to the malignant tumors of animals, but are more like the malformations that may be caused by prolonged irritation. Unlike cancers, they do not represent autonomously growing tissues; the new growth is dependent on the presence of the bacilli, even to the formation of metastases; they show the physiologic functions and changes of the normal tissues from which they are derived, even to the extent of occasionally putting out normal twigs.

H. E. EGGERS.

CANCER MORTALITY IN THE UNMARRIED. S. PELLER, Ztschr. f. Krebsforsch. **30**: 581, 1930.

This statistical study is based on mortality data from Vienna, in large part for the year 1928. It was found that death from cancers were considerably more frequent among married than among unmarried men of corresponding age, although this difference became less in the later years of life. Differences of the same sort, but less in degree, were found for women as well. However, cancer of the breast was almost twice as common in unmarried as in married women, while cancer of the bile tracts, which was much more common in women than in men, was relatively rare in the unmarried women, and in the married women showed an evident relationship to the number of pregnancies. Cancer of the colon, more frequent in men than in women, was somewhat more frequent in unmarried than in married women. In regard to economic status, cancer was more common in the women of the poorer classes than among the more prosperous, but this difference was not shown by men. In general, there was a lower mortality rate for Jews than for gentiles, in spite of the fact that there was a higher rate for intestinal cancer among the former, particularly pancreatic cancer and in the women, mammary cancer.

H. E. EGGERS.

THE TERM PRECANCER. H. STAHR, Ztschr. f. Krebsforsch. **31**:67, 1930.

Stahr takes exception strongly to the current tendency to regard precancerous lesions as constituting definite entities, capable of subdivision into successive stages of progress. He points out that the term covers several dissimilar conceptions: Some of the so-called precancerous changes are really more in the nature of concomitants of cancer, while others are merely indications of the presence of an irritation, which in circumstances that are not yet understood is capable eventually of producing cancer.

H. E. EGGERS.

Medicolegal Pathology

BLOOD GROUPS IN CRIMINAL INVESTIGATIONS. L. S. DYKE, Lancet **1**:1029, 1930.

The determination of blood groups may be of value in cases of disputed paternity, but it has other medicolegal applications as well. In cases of murder or injury it may prove of great importance to determine, if possible, the group of blood on clothing or other objects. Fancy the significance of finding that the blood staining the clothing of the suspect not only does not belong to the blood group of the suspect but does in fact fall in the same group as the blood of the victim. On account of such possibilities it has been urged that the blood groups of all persons involved in crimes associated with bloodshed be determine as promptly as possible. This is said to be customary in Russia.

WOUNDS PRODUCED BY THE PARING-KNIFE (SHOEMAKER'S KNIFE). A. DALLA VOLTA, Arch. di antropol. crim. **49**:56, 1929.

This study supplements the statistical work of Canuto, who two years ago described twenty-five cases (*Arch. di antropol. crim.* **48**:88, 1928). Wounds inflicted by the paring-knife can, under certain circumstances, be differentiated from stab-wounds and cut-wounds produced by other sharp instruments. Peculiarities of these otherwise uncommonly observed wounds are presented by the author in every detail and must be read in the original paper.

E. L. MILOSLAVICH.

Technical

NEW METHOD FOR THE DETERMINATION OF THE BASAL METABOLISM OF BABIES AND OF SMALL CHILDREN. HAROLD L. HIGGINS and VELMA BATES, Am. J. Dis. Child. **39**:71, 1930.

A chamber method for the determination of basal metabolism in babies and small children is described. The advantages claimed for this method are that the periods of observation are much shorter and the results more accurate.

J. N. PATTERSON.

THE MODIFIED ARNETH AND THE SCHILLING BLOOD DIFFERENTIAL COUNTS IN TUBERCULOSIS. H. I. SPECTOR, Am. Rev. Tuberc. **21**:265, 1930.

In comparing the Arneth and the Schilling methods it is apparent that both methods have certain advantages and disadvantages. The Arneth method gives a better understanding of the shifting to the left in progressive infections, and to the right in retrogressive diseases. The Schilling method would fail to detect such an infection, especially in conditions characterized by lymphocytosis. Lymphocytes are an index of resistance while monocytes are an index of the extent of the anatomic lesion and in this respect the Schilling count is superior to the modified Arneth test and is of great prognostic significance since it mirrors the battle field and reflects the intensity of the fight.

H. J. CORPER.

STUDIES ON VITAL STAINING. H. P. SMITH, J. Exper. Med. **51**:369, 1930.

A spectrophotometric method is discussed which permits quantitative analysis of colored substances present in mixtures. Special attention is given to the analysis of mixtures of two dyes which are being used in a series of studies on vital staining. It is shown that the method can be applied to quantitative analysis of mixtures of naturally occurring animal pigments or to mixtures of these with various other colored substances. Certain limitations of the method and certain necessary precautions are discussed.

AUTHOR'S SUMMARY.

PRESERVATION OF RED BLOOD CELLS FOR HEMOLYTIC REACTIONS. GUILFORD B. REED, J. Infect. Dis. **45**:247, 1929.

Placing whole sheep's blood in Rous and Turner's mixture of isotonic dextrose and sodium citrate results in the red cells remaining intact for from eight to twelve weeks. The preservation of the cells is accompanied by gradual increase in resistance to hypotonic sodium chloride and by a decrease in resistance to the hematoxin of *B. welchii* and to complement-amboceptor hemolysis. Attention has been directed to the use of these preserved cells in complement fixation reactions and hematoxin titrations and for the general enrichment of culture mediums. The advantage, for these purposes, is purely one of convenience.

AUTHOR'S SUMMARY.

Society Transactions

CHICAGO PATHOLOGICAL SOCIETY

Regular Meeting, April 14, 1930

HENRY C. SWEANY, *President, in the Chair*

THE INHIBITION OF DIPHTHERIA AND TETANUS TOXINS BY CYSTEINE. ARTHUR LOCKE and E. R. MAIN.

The addition of cysteine to cultures of the diphtheria and the tetanus bacillus is followed by increase in the rate of growth and decrease in the rate of toxin production. Cultures that ordinarily produce 600 and 3,000 minimal lethal doses, respectively, may produce, in the presence of 0.8 per cent cysteine, less than 50 and 100 minimal lethal doses, respectively. The action of the cysteine appears to be directed toward the removal from the culture medium of an essential metallic ion. Evidence is presented that this ion may be Cu^{++}. The copper and iron contents of a highly concentrated preparation of diphtheria toxin are described, together with those of typical aerobic and anaerobic bacteria. The suggestion is made that the bacterial neurotoxins may owe their poisonous character to contents of copper-carrying respiratory substance, well adapted to further the peculiarly aerobic or anaerobic respiratory processes of the bacterial cells in which they have their origin, but intolerable to the cells of the more highly organized, less aerobic or anaerobic tissues into which they may diffuse.

LYMPHANGIOMA OF THE ILEUM. GEORGE MILLES.

The rare occurrence of the so-called lymphangiomas or chylangiomas of the intestine has been emphasized by all authors who have considered the subject. These lesions, usually found incidentally in postmortem examinations, have been discussed by Henke and Lubarsch. They are described as single or multiple, discrete, pea-sized, polypoid excrescences in the mucosa of the upper half of the intestine, occurring in elderly subjects. There are reports of cystic lymphangiomas that have necessitated surgical intervention. Such lesions have occurred in young persons. Reports of occurrence in the bowel have been made by Naumann, Michaelson and Reinecke; in the mesentery, by Rayster and by Abadie and Arguad, and in the omentum, by Graussman and Jaffe and Fischer.

Naumann, in the analysis of his account mentioned that, except for the rare observation of the type described by Henke and Lubarsch, his was the first cystic lymphangioma seen in twelve years at the St. George Hospital, Leipsic. The patient, 23 years old, had pain in the region of the left kidney, increased by lying supine. Obstipation and later symptoms resembling salpingitis were noted. There was a tumor the size of a pigeon's egg in the left fornix. Later, this tumor proved to be a cyst arising from the ileum and adjoining mesentery. The involved loop of intestine and mesentery were resected. The cyst was filled with a chylous fluid containing cholesterol and fats. Microscopically, the tissues were identical with those described in my report, except for the cyst that had penetrated the muscularis.

These tissues were found incidentally during the postmortem examination of a white railroad clerk aged 30 who died from extensive fibrocaseous pulmonary tuberculosis. Meckel's diverticulum, distinct from the tumor under discussion, also was found. A segment of the middle third of the ileum extending 6 cm. in the axis of the intestine was marked off from the remainder of the bowel by its darker and more transparent appearance. Scattered in it beneath the peritoneal surface were irregular white regions as large as 2 mm. in diameter and resembling flecks of cottage cheese. The involved portion on the lumen surface was raised

above the normal mucosa and consisted of closely arranged, soft, sessible, polypoid structures 5 to 10 mm. in diameter. They were light gray-yellow with occasional darker yellow places at the summit of some of the excrescences. Scattered in these tissues were milky white flecks like those on the peritoneal surface.

The polypoid growths had little normal bowel mucosa. The villi, mucosa and submucosa were chiefly spaces as large as 1 mm. in diameter. Nowhere was the muscularis involved. The spaces were lined by flat endothelial cells in a single layer. In the lumina were macrophages filled with fat droplets, and surrounding these cells or occurring alone was a homogeneous lipoid material. The stroma was chiefly loose fibrous tissue, with few cells and some disarranged smooth muscle fibers, the remnants of the muscularis mucosa.

In the classification of this lesion I am uncertain whether it is lymphangioma or lymphangiectasis. Henke and Lubarsch, in discussing the senile variety, preferred to consider them lymphangiectasias rather than true tumors. Histologically, they are like those described in the report by Naumann and the one that I have described. Naumann, from the evidence of progressive growth, preferred to consider the lesion true lymphangioma. The diffuse growth with some evidence of increase in size of the lesion that I have described support Naumann's contention that these are tumors.

Coal Pigmentation of the Liver with Cirrhosis. S. H. Robertson.

The liver to be described was removed by Dr. Apfelbach from the body of a coal miner, aged 35, who died at the Presbyterian Hospital, Chicago, from an abscess of the mediastinum communicating with the thoracic portion of the aorta and the esophagus. The lungs and the tracheobronchial lymph glands contained much coal pigment.

The liver weighed 1,230 Gm. and was firm, and the capsule was everywhere smooth, shiny and transparent. The liver lobules seen through the capsule were irregular in size and shape, from gray-white to gray-red-brown and surrounded by light gray-black regions. These darker regions were associated with about one half of the lobules. The liver cut with slightly increased resistance, and the surfaces made by cutting were moist and glassy and did not bulge. The lobules were distinct, depressed and irregular in size and shape, 3 to 6 mm. in diameter and nearly uniformly surrounded by light gray-black regions in minute white-gray backgrounds. The central veins were distended, and the adjacent liver cells were a darker red-purple than those more peripheral.

The black pigment in sections of the liver remained unchanged when the tissues were placed in concentrated sulphuric acid, in boiling glacial acetic acid, hydrochloric acid, nitric acid, ammonium sulphide and concentrated potassium hydroxide.

Microscopically some of the black pigment was in small deposits between unchanged liver cells and the capillary walls, and a little was contained in the Kupffer cells. The usual distribution of the pigment was within bands and nodules of fibrous tissue. These fibrous regions were sharply circumscribed and never completely surrounded a lobule. They were chiefly in the interlobular tissues, but occurred also around central veins and at any place in a lobule. The pigment and fibrous regions varied in size; many were no longer than six or seven liver cells. The shape of the fibrous patches varied, but there was a general tendency to assume a long, narrow shape following the course of the interlobular vessels or rows of liver cells. These same regions were composed of dense hyaline fibrous tissue with few cells; the cells were chiefly elongated connective tissue cells closely applied to the fibers, and many of them contained black pigment. Fibrous tissue did not occur, except in association with the deposits of pigment.

In about one fourth of the lobules, the central veins were dilated, and there were indistinct liver cells surrounding the veins.

This pigmentation of the liver was associated with a mild interlobular cirrhosis. The chemical tests indicated that the pigment was coal pigment.

William H. Welch (*Bull. Johns Hopkins Hosp.* **1**:32, 1891), described a similar liver. He stated that the character of the fibrous regions and the relationship between them and the coal pigment were the unusual features of the tissues.

Alburger (*Proc. Path. Soc. Philadelphia,* 1905) described the liver of a woman who died from pulmonary tuberculosis, in which there was coal pigmentation but only a slight increase of the interlobular connective tissue.

Small amounts of coal pigment in the liver are not rare. Welch stated that such deposits were reported by Arnold, Soyka, Weigert and others. Weigert demonstrated that adhesions and destructive inflammations may favor the passage of this pigment from the lymph glands directly into adjacent blood vessels and probably similar alterations in the lungs do the same.

Arnold mentioned the frequent association of emphysema of the lungs and coal pigment in the spleen, liver and elsewhere.

DISCUSSION

E. R. LONG: Were deposits of pigment found in the spleen and mesenteric lymph nodes? Deposits in the spleen would suggest dissemination by the blood stream, whereas deposits in the mesenteric lymph nodes could indicate absorption of pigment from the bowel.

S. H. ROBERTSON: There were large deposits of pigment in the spleen, but none in the mesenteric lymph nodes.

MULTIPLE TUMORS OF THE BRAIN IN A CASE OF SYRINGOMYELIA AND SYRINGOBULBIA. F. D. GUNN.

A case of syringomyelia with syringobulbia was presented. Besides cysts lined with endothelial-like cells, multiple tumor formations were found. Adjacent to the cysts, a dense glia meshwork with scanty astrocytes prevailed. This was gradually replaced by glioma formations composed of different types of spongioblasts, astrocytes and astroblasts. Furthermore, papilloma-like protrusions of the wall of the inferior part of the fourth ventricle were found, and a proliferation of ependymal cells with invasion of the nervous tissues. Finally, multiple neurinomas were found at the nerve roots arising from the medulla oblongata.

DISCUSSION

A. KNAPP: Syringomyelia occurs in geographic foci among the working class, more often in men than women. The cord changes may be caused by distention of the canal (hydromyelia), traumatic hemorrhage (hematomyelia) and growth of the glia (neoplastic). Were there sensory disturbances in Dr. Gunn's patient, a thoracic kyphosis or disturbances in swallowing? The changes of cord and brain with syringomyelia sometimes are inconspicuous in the unfixed tissues and are demonstrated only by microscopic examinations.

F. D. GUNN: The clinical record gives no details of sensory disturbances or postural peculiarities.

P. C. BUCY: Syringomyelia is associated with tumors and hyperplasia of the ependyma. A considerable part of Dr. Gunn's tumor seems to consist of ependymal cells. The origin of the endothelial lining of the cysts is difficult to explain. There are wide variations in the cells of tumors of the brain, and sometimes such differences make the classification of a certain tumor difficult. There is never a pure cell tumor, but invariably a mixture, although a certain type of cell may predominate.

STANDARDIZATION OF CHOLESTEROLIZED ALCOHOLIC BEEF HEART ANTIGEN FOR USE IN COMPLEMENT-FIXATION PROCEDURES EMPLOYING WARM PRELIMINARY INCUBATION. B. S. LEVINE.

Only fresh beef heart freshly ground and rapidly dried should be used in the preparation of antigen extracts. The cholesterol content of the antigenic dose

should always be the same for any particular complement-fixation procedure. The antigenic titer for any particular complement-fixation method should be of a fixed value. An antigen used in any particular modification of a complement-fixation method is to be regarded with reasonable assurrance as of the same standard as the one in prior use only after it has yielded 100 positive and 100 negative concordant results. It is evident that standardization of antigens can be done satisfactorily only in laboratories testing a large number of serums routinely.

AN ELECTRICAL DEVICE FOR GRINDING TISSUE UNDER ASEPTIC CONDITIONS. H. O. MARYAN.

There are various devices for grinding tissue under sterile conditions: (1) the mortar, pestle and sand; (2) Latipie's hand tissue-grinder; (3) Hirschfelder, Rosenow and Nickel's tissue-crushers, and (4) Rosenow's sterile air chamber containing a mortar, pestle, sand and small meat-grinder. Dr. Maryan found that by these methods there were unavoidable sources of contamination through handling and the great difficulty of finely crushing the fibrous tissues. Therefore, a mortar driven tissue-grinder was devised, enclosed in a vertical tubular brass air chamber. The details of construction may be obtained from E. V. Muller & Company, Chicago.

Regular Monthly Meeting, May 12, 1930

HENRY C. SWEANY, *President, in the Chair*

INTRACRANIAL NEOPLASMS IN LOWER ANIMALS. MAUD SLYE, HARRIET F. HOLMES and H. GIDEON WELLS.

A review of the literature indicates that intracranial tumors are rarely observed in lower animals of any species. Especially noteworthy is the fact that but one seemingly conclusive report of a cerebral glioma in an animal could be found. In 11,188 brains of mice of the Slye stock, only three primary intracranial neoplasms were found, namely, an endothelioma of a cerebral peduncle; a papillomatous growth in the ependyma of the lateral ventricle, and an infiltrating adenoma of the hypophysis. Although about half the mice examined suffered from some sort of malignant tumor, in no case was an intracranial metastasis found, although in two cases of osteosarcoma, metastases were found in the skull. A case of adenoma in the hypophysis of a parrakeet (*Agatornis pullaria*) is also described.

MALIGNANT MIXED TUMOR OF THE THYROID GLAND WITH SKELETAL MUSCLE FIBERS. EDWIN F. HIRSCH.

Spindle cells with the cross-striations of skeletal muscle fibers in malignant mixed tumors of the thyroid gland seem not to have been reported. A primary malignant tumor of the thyroid producing metastases into many tissues of the neck, trunk and bones occurred in a young man, aged 21, and in all of the growths there were mixtures of three varieties of cells, namely; small undifferentiated cells, large spindle cells with cross-striations of skeletal muscle fibers, and huge fused-cell aggregates suggesting abortive thyroid gland acini.

DISCUSSION

H. G. WELLS: In the metastases of these malignant mixed tumors there is often a separation of the two germ layer components.

MULTIPLE PULMONARY ABSCESSES SIMULATING TUBERCULOSIS CAUSED BY FRIEDLÄNDER BACILLUS. H. C. SWEANY, ASYA STADNICHENKO and KARL J. HENRICHSEN.

The clinical course, pathologic and bacteriologic observations in a fatal Friedländer bacillus infection were described. The micro-organism differed from the usual type in that it grew as well or better anaerobically than aerobically, poorly on potato medium, fermented dextrose with acid and gas, and produced coagulation.

The process was subacute or chronic bronchopneumonia with progressive necrosis and abscess formation with a varied type of cell reaction from lymphocytes, monocytes and plasma cells to polymorphonuclear leukocytes.

The clinical aspects and roentgen appearances closely simulated chronic pulmonary tuberculosis, differing only in the general appearance of the patient and in the irregular type of temperature.

CYSTADENOMA OF THE GALLBLADDER. RALPH A. KORDENAT.

Cystadenomas of the gallbladder are usually found in women, of the average age of 40 years, complaining of symptoms of cholecystitis and cholelithiasis. The tumors are rare, usually occurring in the fundus of the gallbladder. They are small (1.5 cm. in diameter in the instance here reported). They appear grossly as a rounded, oval elevation of a limited area of the fundus. Microscopically, there are glandular acini lined with adult type of columnar epithelium without degenerative changes or evidence of reversion to the embryonic type. The etiology of these tumors is not clear.

DISCUSSION

E. F. HIRSCH: These tissues are probably inflammatory hyperplasias and not true tumors.

PATHOLOGICAL SOCIETY OF PHILADELPHIA

Regular Meeting, May 9, 1930

BALDWIN LUCKE, *President, in the Chair*

SIX CARD SPECIMENS OF COMPARATIVE SIGNIFICANCE. HERBERT RATCLIFFE.

The following specimens were presented: an inguinal hernia in a pig-tailed *macaque;* spondylitis deformans in a léche antelope; ulcerative cholecystitis with cholelithiasis in an orang-utan; the spleen and kidneys of a cheetah showing unusual infiltrations in myeloid leukemia, and arteriosclerosis in a greater bird of paradise and in a California hair seal. These specimens were taken from routine autopsy material at the Philadelphia Zoological Garden and illustrate a not widely recognized fact, namely, that wild animals in captivity regularly show disease changes similar to those of man.

A CASE OF ACUTE LEUKEMIA WITH AUTOPSY. B. L. CRAWFORD.

History.—On Feb. 6, 1930, a white boy, aged 14, was admitted to Jefferson Hospital (service of Dr. Gibbon; later transferred to that of Dr. McCrae), with swelling of the neck, more marked on the left side. The family history was negative. The patient had enjoyed good health prior to July, 1929. In this month he had an attack of sore throat, lasting about one week. Shortly afterward, on one side, the neck, face and eye became swollen over night. The swelling in the neck did not disappear, and when, shortly afterward, incision was made, approximately two teaspoonfuls of pus were obtained. The swelling practically disappeared, but the father noted that the boy was not as vigorous or active as he had been previously, tiring easily on exertion. In November, marked swelling of the face, neck and gums followed extraction of a tooth and the patient gradually grew worse, with loss of weight and strength.

Physical Examination.—The results of physical examination were negative, except for marked gingivitis, swelling of the gums and of both sides of the neck. The temperature ranged from 99 F. to 105 F. The blood count on admission was: hemoglobin (Dare) 42 per cent; erythrocytes, 2,700,000; leukocytes, 22,600; color index, 0.77 plus. The differential count was: polymorphonuclears, 6 per cent; small lymphocytes, 16 per cent, and large mononuclear, immature cells 78 per cent. These large mononuclear cells had large, irregularly shaped nuclei, some of which contained nucleoli, and the cytoplasm of many of cells was finely granular. Practically all these mononuclear cells contained oxydase-positive granules. There was also marked change in the red blood cells, with presence of a few normoblasts and an occasional megaloblast. A short time before death, the leukocyte count decreased to 11,800. The results of the Wassermann and Kahn test, of the blood were negative.

Bacteriologic Studies.—Two blood cultures remained sterile. Smears from the mouth contained many organisms, including many spirochetes and fusiform bacilli. Cultures from the lesion in the neck on one occasion contained *Staphylococcus albus* and *Staph. aureus,* and on one occasion when the lesion was incised, a mixed growth of *Staph. albus* and nonhemolytic *Streptococcus* was obtained.

Autopsy.—Autopsy was performed seven hours post mortem. The gums were swollen, soft and spongy, and the teeth were in bad condition, but there was no definite ulceration of the mouth. The subcutaneous tissue of the neck was swollen, nodular and edematous. The pericardium and pleura contained numerous small petechial hemorrhages. The lungs contained numerous, firm, circumscribed, consolidated areas throughout all the lobes. The spleen weighed 300 Gm., and was uniform in color and consistency. The cut surface was red, smooth and resilient. Follicles were not observed. A few enlarged, rather soft lymph nodes were present at the base of the neck, in the mediastinum and in the upper part of the abdomen. No nodules were observed in either the spleen or the liver. The bone-marrow of the lower end of the femur was markedly hyperplastic, friable and red.

Histologic Examination.—Sections from the lymph nodes, spleen, lungs and liver revealed a diffuse infiltration of these organs by large mononuclear cells with large, irregularly shaped nuclei. In sections from the bone-marrow, the leukoblastic hyperplasia seemed to overshadow the erythroblastic element.

Summary.—From the presence of the immature type of cell (granulocyte) in the blood, the rapidly fatal course of the illness and the infiltration of the internal organs by the large immature type of cell the diagnosis of acute myeloid leukemia was considered justified.

THE RELATIVE PHAGOCYTIC ABILITY OF MONOCYTES AND POLYMORPHONUCLEARS. M. STRUMIA, B. LUCKE, S. MUDD and M. MCCUTCHEON.

Results of experiments in which various antigens were employed *(Bacillus tuberculosis, B. coli,* sheep erythrocytes, collodion particles coated with various proteins, etc.) show that serums and their fractions, immune or not, promote phagocytosis by both monocytes and polymorphonuclears in vitro. There is a close parallelism in the phagocytosis-promoting effect of serums on the two kinds of cells. The dilution of immune serum causing the greatest degree of phagocytosis in one kind of cell also causes the greatest degree of phagocytosis in the other. Conversely, when a given dilution of serum does not induce phagocytosis in one kind of cell, it also fails to cause phagocytosis in the other. The degree of spontaneous phagocytosis is different with the various particles.

SURVEY OF THE HISTORY OF THE LABORATORY OF COMPARATIVE PATHOLOGY OF THE PHILADELPHIA ZOOLOGICAL GARDEN. COMPARABLE DISEASES OF MAN AND WILD ANIMALS. HERBERT FOX.

The survey included: remarks in response to the request of the president about the origin and history of the Laboratory of Comparative Pathology of the

Zoological Society of Philadelphia; descriptions of the main events that have occurred in the twenty-five years of the laboratory's existence, and a special reference to the experience of eradicating tuberculosis in monkeys by the use of the tuberculin test. Details of these parts have been published.

Since the eradication of tuberculosis, the total death rate of monkeys falls almost uninterruptedly and falls disproportionately faster than the death rate of tuberculosis. The expectation of life of all animals has increased 130 per cent. The expectation of life of nontuberculous animals has increased 100 per cent. This would indicate that the removal of tuberculosis, not only eliminates this cause of death, but seems to be parallel with the improvement of life expectancy of all animals. Morbidity and mortality from other causes remain about the same with a slight increase in certain varieties of enteritis and degenerative bone disease.

Figures indicate again the susceptibility of old world monkeys to tuberculosis, a definitely lower susceptibility of South American monkeys and marked resistance of marmosets.

The subcutaneous injection of tuberculin remains the best method of making the tuberculin test. Cutaneous, intracutaneous and conjunctival tests are difficult to perform and the results are unreliable.

A proper cage, an experienced handler and a knowledge of the normal temperature of monkeys are essential to the success of the test.

Contrastive Diseases.—It is interesting to note that captive wild animals do not show clinical and pathologic evidence of rheumatic infection. Microscopic structures comparable to the Aschoff body have been seen in a variety of mammals in the absence of arthritis, valvulitis and cutaneous lesions.

The pathology of hypertension is not unequivocal, but if the condition can be described as chronic myocardial and valvular disease, arteriosclerosis or arteriolitis, chronic nephritis, uremia and lesions of the central nervous system, it is noteworthy that this combination is exceedingly rare, and it is therefore probable that hypertension, essential at least, does not occur in wild animals.

There are few criteria on which to judge the existence of hypersensitivity. If emphysema and asthenia are major indications, hypersensitivity must be exceedingly rare. So, too, skin eruptions of the sensitivity type are exceedingly rare.

Bronchiectasis is another rarity among wild animals. Chronic bronchitis and peribronchitis are reasonably common, especially among the carnivores and rodents. It is probable that lower animals do not have bronchiectasis because they do not indulge in fits of coughing with the marked inspiratory increase of pulmonary pressure and the distension of the lungs by forceful expiration.

Degenerative disease of the nervous system of the tabes type and apoplexy are practically unknown. Degenerative myelitis on the basis of malnutrition has been observed in the ungulates.

DIET IN RELATION TO THE DEGENERATIVE BONE DISEASES IN MONKEYS. E. P. CORSON-WHITE.

In the course of a study of the degenerative bone diseases, an analysis of the diets fed in the Gardens to the various groups of monkeys was made, especial note being made of the amount of protein, calcium and phosphorus. This analysis, when reduced to the amount per kilogram of body weight per day for each variety, divided the monkeys into several groups: (1) those in which the protein, phosphorus and calcium were equal to or above the amount of these substances (per kilogram of body weight per day) necessary to keep man in equilibrium; (2) those in which the protein fell below, but in which the calcium and phosphorus were above man's requirement for maintenance; (3) those in which both protein and calcium were below, but in which phosphorus was above, and (4) those in which the protein and the calcium were still below, and the phosphorus was either just at or below, man's requirements for maintenance.

In these groups, the degenerative bone diseases were definitely distributed. In class 1 osteomalacia and hypertrophic osteitis rarely if ever occurred. At times young were born and developed on mother's milk without the occurrence of rickets, even when confined to the house. In class 2 osteomalacia and osteitis were rare, and when present, were slight in extent. The young that were born, if fed on mother's milk, developed more or less severe rickets. Class 3 showed some osteomalacia, which was never severe. Young were born, but generally died early, and almost always, if they lived for any time, showed severe rickets. Class 4 was apparently unable to maintain inorganic equilibrium. They showed a high incidence of osteomalacia of a severe progressive type. Hypertrophic osteitis also was present. Young were never born, and the animals made no attempt at breeding.

From this study it was concluded: that diet, if not a cause of degenerative bone diseases, was at least a potent factor in their development; that the amount of protein, calcium or phosphorus per kilogram of body weight per day necessary to maintain man in equilibrium was the amount necessary to keep the other primates in equilibrium, and that the standard requirement of calcium, protein and phosphorus for maintenance of balance was probably the same in all primates.

Book Reviews

A Classification of Bright's Disease. By Dorothy S. Russell. Price, 8 shillings, 6 pence. Pp. 248, with 16 plates, 2 in color. Special Report Series, No. 142, Medical Research Council of Great Britain. London: His Majesty's Stationery Office, 1929.

The soundness of Richard Bright's views on the gross pathologic anatomy of the kidney and on the relation of renal pathology to the clinical state of the individual during life is attested by the fact that they still form the basis of text-book discussions of renal disease and that the classifications of nephritis attempted since the appearance of Bright's studies in 1836 have had to justify themselves in the light of his work. New terms, like nephrosis and nephropathy, have been introduced and have been widely accepted. They are sometimes used in such a way as to suggest that the writer does not have in mind a clear conception of the underlying renal pathology. Their use has led to renewed philosophic discussion of the nature of inflammation as a general pathologic process. In this discussion there is evident as wide a divergence of opinion in the interpretation of parenchymatous alterations as inflammatory reactions as in the identity or nonidentity of nephrosis and nephritis. Other classifications have sought to introduce greater precision into renal pathology by the use of microscopic data that were not available to Bright.

The present study is an attempt at classification based primarily on microscopic data. It is, as the title indicates, a classification of Bright's disease. Since the present concept of renal pathology may not include under Bright's disease all of the conditions originally described by Bright, it is necessary and proper that the author define the Bright's disease that she proposes to discuss. This she does in the following words: "In this paper Bright's disease is defined provisionally as an idiopathic, non-suppurative inflammation of the kidneys. Those forms of nephritis that are clearly symptomatic are treated separately." As thus defined and used, Bright's disease is therefore not synonomous with nephritis, a fact that makes for difficulty in reading, since the reader may have in mind his own broader conception of nephritis, whereas the author has limited herself to a portion of the field that she terms Bright's disease. The liability to confusion is increased by the fact that forms of nephritis, other than those falling within the restricted definition of Bright's disease, are discussed in a comparative manner. On this point the author says: "Inasmuch as all non-purulent inflammations of the kidney met with in this investigation have been described as examples either of Bright's disease or of symptomatic nephritis, and the histological changes in both groups have been compared, readers can modify our definition of Bright's disease as they wish."

A brief introductory chapter is followed by one of thirty-seven pages which is virtually a microscopic microdissection of the kidney. The various alterations encountered in the glomeruli, the tubules, the interstitial tissue and the vessels are described with great minuteness. Especial attention is given to the glomerulus, which is dissected into the endothelium and stroma of the tuft, the visceral and parietal epithelium and basement membrane of the capsule, the periglomerular tissue and the cavity. In the discussion of "progressive changes leading to partial or complete obliteration of the capsular space and destruction of the tuft," a sharp distinction is made between "ischaemic glomerular atrophy" and "toxic glomerular atrophy," this distinction being a fundamental one in all the discussion that follows and in the final classification adopted.

There next follows a chapter in which the various minute lesions described in the preceding chapter are put together, correlated and described in relation to each other as they occur in the kidney as a whole. The elements of the

classification ultimately adopted begin to make their appearance in the division of the kidneys of Bright's disease into histologic types dependent on whether the inflammatory reaction is early, intermediate or late. In each group there is further subdivision according to whether the reaction is mild or intense. In the group with late inflammatory changes, alterations of toxic origin are distinguished from those of ischemic origin, the two kinds of lesion often being combined. The gross appearances are correlated with the histologic alterations in the various types of kidneys.

In chapter IV, entitled "Histological Types of Kidneys in Symptomatic Nephritis," "forms of nephritis which are found in association with various pathological conditions and are apparently symptomatic of them are described and compared with the different types in Bright's disease." It is difficult to understand the rationale of differentiating between the nephritis of a long list of diseases, infectious and otherwise, and the nephritis of Bright's disease, especially that form which the author terms toxic. The reasons for such a differentiation are set forth in chapter V, "The Nature of Ischaemic and of Toxic Nephritis in Bright's Disease." In order not to be led too far afield in the realm of argumentation, one may grant the validity of terming ischemic the type of renal change that is associated with degenerative arterial changes, concerning which form "there can be little doubt that it is due to interference with the blood supply." But the following summarizing statement on toxic nephritis does not leave one much the wiser as to the essential differences between toxic nephritis of Bright's disease and symptomatic nephritis of a host of other diseases: "It is clear that varieties of nephritis resembling the varieties of the toxic nephritis of Bright's disease can be caused by endogenous and bacterial poisons. The term 'toxic' appears, therefore, to be amply justified for this an-ischaemic form of Bright's disease."

The two succeeding chapters discuss, respectively, the clinical manifestations of the nephritis of Bright's disease classified by the histologic criteria adopted by the author and an evaluation of the histologic classification on the basis of clinical evidence. The classification proposed is homologized with a clinical terminology as follows (the clinical terminology has been placed in parentheses to prevent confusion): I, Primary ischaemic nephritis (primary arteriosclerotic nephritis). II, Toxic nephritis: 1, nephritis mitis (subacute hydropigenous nephritis); 2, nephritis acris in (*a*) early stage (acute nephritis), (*b*) intermediate stage (subacute azotemic nephritis), (*c*) chronic stage (chronic azotemic nephritis); 3, nephritis repens (insidious chronic azotemic nephritis).

A brief summarizing chapter that restates the author's views concludes the body of the monograph. In one appendix are given the results of the renal efficiency tests, the cases being grouped according to the author's classification. In another appendix are presented concise summaries of the clinical and anatomic observations of the 123 necropsies that formed the basis of the work. There is a bibliography of fifty-one titles. A synopsis at the head of each chapter and subtitles in the body of the chapter facilitate reading. A large number of cross references in the text to other parts of the work make for ease of reference but also for difficulty in reading.

The monograph presents in great detail the results of a careful histologic study of the kidney in certain forms of nephritis and attempts to correlate the clinical manifestations of such forms of nephritis with the histologic changes that form the basis of the classification adopted. That the classification and terminology proposed will soon replace other recent classifications or terms introduced by Bright and in use ever since appears doubtful.

THE AUTONOMIC NERVOUS SYSTEM. By ALBERT KUNTZ, PH.D., M.D., Professor of Anatomy, St. Louis University School of Medicine. Price, $7 net. Pp. 576, with 70 engravings. Philadelphia: Lea & Febiger, 1929.

The great significance of the autonomic nervous system both in health and in disease is becoming more and more apparent; however, a number of difficulties

confront the physician who wishes to orient himself with respect to the available scientific data on the subject. From the clinical as well as the experimental aspects there is an enormous literature, which is to a large extent uncorrelated. The discovery of new facts has repeatedly made it necessary to give up wide generalizations previously accepted, such, for example, as the original formulations of vagotonia and of sympathicotonia. Even in terminology the various authors are not in complete agreement, so that a certain confusion of terms results. Of course, a considerable part of the difficulty encountered by the clinician or the experimental investigator in any attempt to survey the field of the functions and the disorders of the autonomic nervous system is due to the still imperfect knowledge of that subject. But it cannot be denied that there has been a neeed for a comprehensive treatise on the vegetative nervous system. Such a need is now answered by Kuntz in his book on the autonomic nervous system.

The author follows with only minor deviations the terminology of Langley, using the terms autonomic, sympathetic and parasympathetic. The introduction contains a brief presentation of the historical development of general views concerning the autonomic nervous system, as they are so well reflected in the terminology itself: the involuntary nerves; the great, medium and small sympathetics of Winslow (1732); the ganglionic nervous system of Johnstone (1764); the vegetative system of Bichat, who made a distinction between animal life and organic or vegetative life in the organism, and accordingly assumed the existence of animal and vegetative nerves (1800); Gaskell's classification of the visceral nervous system; Langley's "autonomic nervous system," a term introduced on the basis of physiologic and pharmacologic research.

The first part of the book deals with the anatomy and physiology of the autonomic nervous system: the macroscopic structure; the histology of the autonomic ganglion cells; the "fiber anatomy" of the autonomic system — autonomic centers and conduction pathways; the general physiology of the autonomic system, with special treatment of the relationships to endocrine glands and of pharmacologic influences on the sympathetic and parasympathetic nerves; the development of the autonomic nervous system.

The second part considers the relationships of vegetative innervation to the special systems of the organism: the circulatory system, the respiratory system, the digestive system, the glands (including glands of internal secretion), the genitourinary organs and the involuntary innervation of the eye. A special chapter is devoted to the difficult problems of the autonomic innervation of the skeletal muscles.

In the third part the pathology of the autonomic system is treated. First, the pathologic anatomy, especially the microscopic changes, is discussed, including neoplasms of the vegetative system. There follows a survey of the whole subject of visceral sensitivity and the clinically important topic of referred pain. The conception of vagotonia-sympathicotonia is outlined in a special chapter. In the last two chapters the pathologic aspects of the subject are considered from a more nosologic point of view, and a survey of the surgery of the autonomic system is made.

It is apparent that the author writes with a full knowledge of his subject. This is especially evident in those sections which he has enriched by his own researches, notably the problem of autonomic innervation of skeletal muscles and the outline of the ontogenetic and phylogenetic development of the autonomic system. There is an excellent, comprehensive bibliography. In a book dealing with one of the most problematic divisions of neurology, one may see a number of points in a different light from the author. Such controversial subjects can be settled only by further factual investigations. As a guide to just such further research, this book should be of great use. It is not only the best book available in English on the subject, but it is a useful and important addition to such standard works as those by L. R. Müller, Schilf and Laignel-Lavastine.

FILTRABLE VIRUSES AND RICKETTSIA DISEASES. By EARL BALDWIN MCKINLEY. Price, $4. Pp. 442, with 70 plates and 7 text figures. Manila: Bureau of Science, 1929.

This book is monograph 27 of the Bureau of Science, Manila, and is reprinted from the *Philippine Journal of Science*, volume 38, 1929. It gives a review of the knowledge of the large group of diseases of man, animals of all kinds or plants that are either accepted or tentatively regarded as caused by ultramicroscopic or filtrable viruses. In this group the diseases of man receive particular attention. As indicated by the title, the diseases known or thought to be caused by *Rickettsia* are included in the review. Since the book was published, psittacosis has been shown fairly conclusively to be caused by a filtrable virus. McKinley's review is intentionally descriptive rather than analytic or critical, and shows the present state of knowledge on a given topic, e. g., bacteriophage, or at least the general trend of the developments in active investigation. Chapter 18, the final chapter, discusses more critically certain general phases of the virus diseases.

The book is illustrated extensively by the reproduction of seventy plates from original articles, which is a highly helpful feature. Each chapter is provided with a selected bibliography. The author's intention to revise and expand the review, as developments may indicate, merits encouragement.

Books Received

FILTERABLE VIRUS AND RICKETTSIA DISEASES. By Earl Baldwin McKinley. Price, $4.00 bound; $2.50 unbound. Pp. 442, with 70 plates and 7 text figures. Manila: Bureau of Science, 1929.

TRAUMA, DISEASE, COMPENSATION: A HANDBOOK OF THEIR MEDICO-LEGAL RELATIONS. By A. J. Fraser, M.D., Chief Medical Officer, Workmen's Compensation Board, Winnipeg. Price, $6.50. Pp. 524. Philadelphia: F. A. Davis Company, 1930.

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CHILD LIFE INVESTIGATIONS: THE CAUSES OF NEO-NATAL DEATH. By J. N. Cruickshank, Medical Research Council Special Report Series, no. 145. Price, 1 shilling, 6 pence, net. Pp. 87. London: His Majesty's Stationery Office, 1930.

THE ROAD TO HEALTH. By C.-E. A. WINSLOW, D. P. H., Professor of Public Health, Yale School of Medicine. Price, $2. Pp. 151. New York: The Macmillan Company, 1929.

THE BACTERIOPHAGE AND ITS CLINICAL APPLICATIONS. By F. D'Herelle, Professor of Bacteriology, Yale University School of Medicine. Translated by George H. Smith, Professor of Immunology, Yale University School of Medicine. Price, $4. Pp. 258. Springfield, Ill.: Charles C. Thomas, 1930.

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